Synthesis of polar aminosulfonamide ligands and their application in enantioselective transfer hydrogenation

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Synthesis of Polar Aminosulfonamide Ligands and their Application in Enantioselective Transfer Hydrogenation

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Synopsis

Techniques for the immobilisation or 'heterogenisation' of homogeneous catalysts are currently of great interest. This is a consequence of the ever increasing demand for efficient and environmentally friendly catalytic systems. Whilst there have been many trials to immobilise homogeneous catalysts on solid supports, successful examples are rare. The application of homogeneous catalysts in aqueous solution is more feasible; results from biphasic and supported aqueous phase catalytic systems are encouraging. These techniques may offer the opportunity to perform homogeneous catalytic reactions in a manner which is appealing from economic and environmental aspects.

Catalytic asymmetric transfer hydrogenation of ketones has recently emerged as a attractive means of synthesising enantiomerically enriched alcohols, which are useful building blocks for organic synthesis or may be valuable products in their own right. This alternative method of asymmetric reduction is appealing because it utilises cheap, readily available and easily handled, liquid reductants such as 2-propanol. Over the last decade, extensive studies have led to the development of highly effective homogeneous transfer hydrogenation catalysts. In particular, Noyori has introduced a ruthenium catalyst bearing an enantiomerically pure mono-*N*-tosylated diphenylethylenediamine ligand.

This thesis describes the synthesis of polar analogues of mono-N-tosylated diamine ligands and demonstrates their application in enantioselective hydrogen transfer reactions under aqueous conditions.

Chapter 1 reviews the relevant areas of chemistry. That is, ligands which impart water-solubility to an organometallic complex; the asymmetric reduction of ketones with particular emphasis on enantioselective transfer reduction; and the use of biphasic and supported aqueous phase catalysis as techniques for the heterogenisation of homogeneous catalysts.

The first section of Chapter 2 describes the synthesis of enantiomerically pure, polar analogues of Noyori's *N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine and Knochel's *N*-(*p*-tolylsulfonyl)-1,2-diaminocyclohexane ligands. Subsequent sections detail the application of these in the ruthenium, rhodium and iridium-catalysed asymmetric transfer reduction of aromatic ketones, under aqueous conditions. The third section briefly examines the implementation of these novel ligands in biphasic and supported aqueous phase transfer hydrogenation systems.[118]

Acknowledgements

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Abbreviations

AA	atomic absorption
Ac	acetyl
acac	acetylacetonate anion
AMPHOS (iodide)	2-(diphenylphosphino)ethyltrimethylammonium iodide
app. s	apparent singlet
app. t	apparent triplet
app. td	apparent triplet of doublets
aq.	aqueous
Ar	aryl
atm	atmosphere
BDPP	2,4-bis(diphenylphosphino)pentane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINAS-Na	octasodium salt of 2,2'-bis[methyl(sulfophenyl)phosphine diyl]-1,1'-binaphthaline-4,4',7,7'-octasulfonic acid
Boc	*tert*-butoxycarbonyl
br s	broad singlet
Bu	butyl
cat.	catalyst/catalytic
Chiraphos	2,3-bis(diphenylphosphino)butane
conc.	concentrated
Conv.	conversion
CPG	controlled pore glass
CYCLOBUTANEDIOP	1,2-bis[(diphenylphosphino)methyl]cyclobutane
CYDN	*trans*-1,2-diaminocyclohexane
d	doublet
DCM	dichloromethane
dd	doublet of doublets
ddd	double doublet of doublets
DH_2	hydrogen donor
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl phosphino)butane
DMF	*N*,*N*-dimethylformamide

DMSO	dimethyl sulfoxide
DPEN	1,2-diphenylethylenediamine
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
ent	enantiomer
equ.	equivalents
ES	electrospray
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
FT-IR	Fourier transform infrared
GC	gas chromatography
h	hours
ICP-MS	inductively coupled plasma mass spectroscopy
IR	infrared
m/z	mass/charge
Me	methyl
MeOH	methanol
min	minute
mmol	millimole
mol	mole
mp	melting point
MPV	Meerwein-Ponndorf-Verley
NMR	nuclear magnetic resonance
NORBOS-Na	trisodium salt of 3,4-dimethyl-2,5,6-tris(p-sulfonatophenyl)-1-phosphanorbornadiene
Oleum	fuming sulfuric acid ($H_2SO_4.xSO_3$)
Ph	phenyl
ppm	parts per million
Rac	racemic
Rac-DPEN	racemic 1,2-diphenylethylenediamine
Ref.	reference

ROMP	ring opening metathesis polymerisation
rt	room temperature
s	singlet
S/C	substrate/catalyst
SAP	supported aqueous phase
SAPC	supported aqueous phase catalysis
select.	selectivity
t	triplet
TBAHS	tetra-*n*-butylammonium hydrogen sulfate
THF	tetrahydrofuran
TOF	turn-over frequency
TPP	triphenylphosphine
TPPDS-Na	disodium 3-[phenyl(3-sulfonatophenyl)phosphino]benzene sulfonate
TPPMS-Na	sodium 3-(diphenylphosphino)benzenesulfonate
TPPTS-Na	trisodium 3-[bis(3-sulfonatophenyl)phosphino]benzene sulfonate
Ts	p-toluenesulfonyl
UV	ultraviolet
VASO 67 (AIBN)	2,2'-azobis(*iso*-butyronitrile)

Success is the ability to go from one failure to another with no loss of enthusiasm.

Sir Winston Churchill

Chapter 1

Introduction

1.1 Ligands for Water-Solubilising Organometallic Compounds

1.1.1 Catalysis in Aqueous Media

Organometallic catalysis in aqueous systems has been actively studied over recent years.[1] Intense interest developed in this area following the introduction of the successful Ruhrchemie/Rhône Poulenc[2] oxo process in 1984, which utilises water-soluble rhodium catalysts in the hydroformylation of propene. The use of an aqueous phase in a reaction containing an organometallic catalyst complex is not necessarily obvious. As Cintas[3] wrote,

"*At first, the idea of performing organometallic reactions in water might seem ridiculous, since it goes against the traditional belief that most organometallics are extremely sensitive to traces of air and moisture and rapidly decompose in water.*"

This belief arose because the majority of significant and industrially important organometallics, such as the cobalt hydroformylation catalysts, had sensitivities that required stringent handling techniques for the exclusion of water or air. However, since the early 1980's there have been numerous publications and patents demonstrating that many organometallic compounds are compatible with aqueous media.

The use of an aqueous phase containing an organometallic catalyst holds several advantages. Primarily, the problem of catalyst and product separation that is usually associated with homogeneous catalysis is easily resolved; the high polarity of water allows easy separation from non-polar solvents or products. In addition to this, using water as a solvent has many other industrially and environmentally attractive benefits; it is cheap and widely available in suitable quality, it is non-flammable, non-toxic, odourless and colourless. Also, the physical properties of water (such as, its high polarity, its amphoteric nature and its strong propensity to involve hydrogen bond interactions) may combine to produce unexpected reaction rates and selectivities.

Therefore, since the realisation that aqueous catalysis has much to offer, a significant amount of research has been undertaken in the development of water-soluble organometallic catalysts that take advantage of the unique properties of water.

1.1.2 Design of Water-Soluble Catalysts

Organometallic complexes gain water-solubility by two means:

- Through the complexation of the metal with a water-soluble ligand; and
- By the direct interaction of water with the metal centre.

The majority of work undertaken in the development of water-soluble catalysts centres on the modification of established ligands to make them water-soluble. This is usually achieved by the incorporation of ionic or polar substituents such as sulfonate, carboxylate, ammonium and hydroxyl groups. For example, the substitution of a triphenylphosphine ligand for a sulfonated triphenylphosphine ligand usually imparts water-solubility to the metal complex.

The last decade has seen the development of organic-soluble catalysts with exceptional activities and selectivities. This has been achieved by the systematic modification of ligand properties, such as the alteration of peripheral functionalities or chiral elements. This process has led to the formation of an extensive library of ligands that may be utilised in the construction of catalysts. Most of the work carried out on the synthesis of water-soluble catalysts has taken refined examples from this library and attempted to render them water-soluble; the expectation being that the resulting catalyst complexes will demonstrate comparable (or enhanced) properties to that of the organic-soluble counterparts. Modification of a ligand to make it more polar will alter its electronic and steric properties, and hence may alter the activity and selectivity of the catalyst complex to which it is coordinated.

1.1.3 Water-Soluble Ligands

Figure 1 shows the various categories into which water-soluble ligands may be arranged. The following discussion will focus on one or two examples from each category.

1.1.3.1 Phosphines[4]

Undoubtedly, phosphines are the most popular class of ligand. Phosphines are found in many catalytically active organometallic species, and are therefore attractive targets for rendering a complex water-soluble. Indeed, hydrophilic phosphines now constitute the largest class of water-soluble ligand.

Anionic Phosphines: Included in this class are phosphines containing sulfonate, carboxylate and phosphonate functionalities.

Sulfonated Phosphines

Sulfonated phosphines (Figure 2) are the most commonly used class of ligand for the formation of water-soluble metal complexes. In particular, the trisulfonated derivative of triphenylphosphine[5] (TPPTS-Na) **1** appears most frequently, in combination with a variety of metals. The rhodium(I) complex, $HRh(CO)(\mathbf{1})_3$, was the original catalyst at the centre of the industrially important Ruhrchemie/Rhône Poulenc biphasic hydroformylation process. However, as homogeneous catalysis has progressed and new tailored phosphine ligands have emerged, TPPTS-Na has been replaced by ligands that give rise to catalysts with higher activities and selectivities. The use of ligands such as the bicyclic phosphine **2** (NORBOS-Na)[6] and the bidentate diphosphine **3** (BINAS-Na)[7] have led to dramatic improvements in terms of activity and selectivity for the hydroformylation of propene on an industrial scale. Tetrasulfonated BINAP **4** was used by Davis *et al.* in the formation of a supported aqueous phase catalyst. The ruthenium(II) complex, $[ClRu(C_6H_6)(\mathbf{4})]Cl$ was successfully utilized for the asymmetric hydrogenation

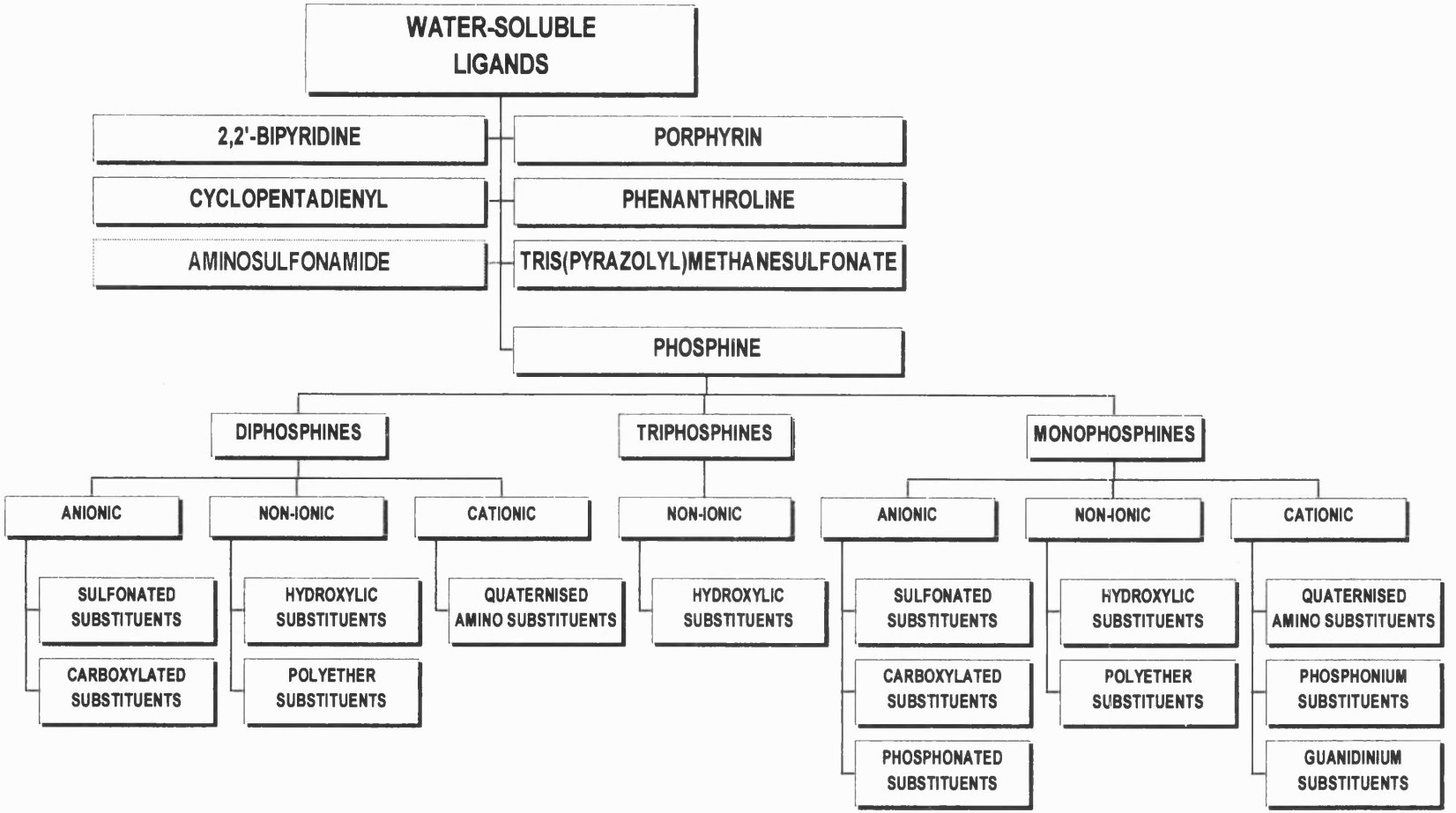


Figure 1. Classification of water-soluble ligands.

of 2-(6'-methoxy-2'naphthyl)acrylic acid to (*S*)-naproxen[8] (discussed further in section 2.4). Rhodium(I) catalysts containing chelating diphosphines **5** (tetrasulfonated (*S,S*)-CYCLOBUTANEDIOP) and **6** (tetrasulfonated (*S,S*)-BDPP) were utilised for the asymmetric hydrogenation of carbon-carbon, carbon-oxygen and carbon-nitrogen double bonds under biphasic conditions.[9]

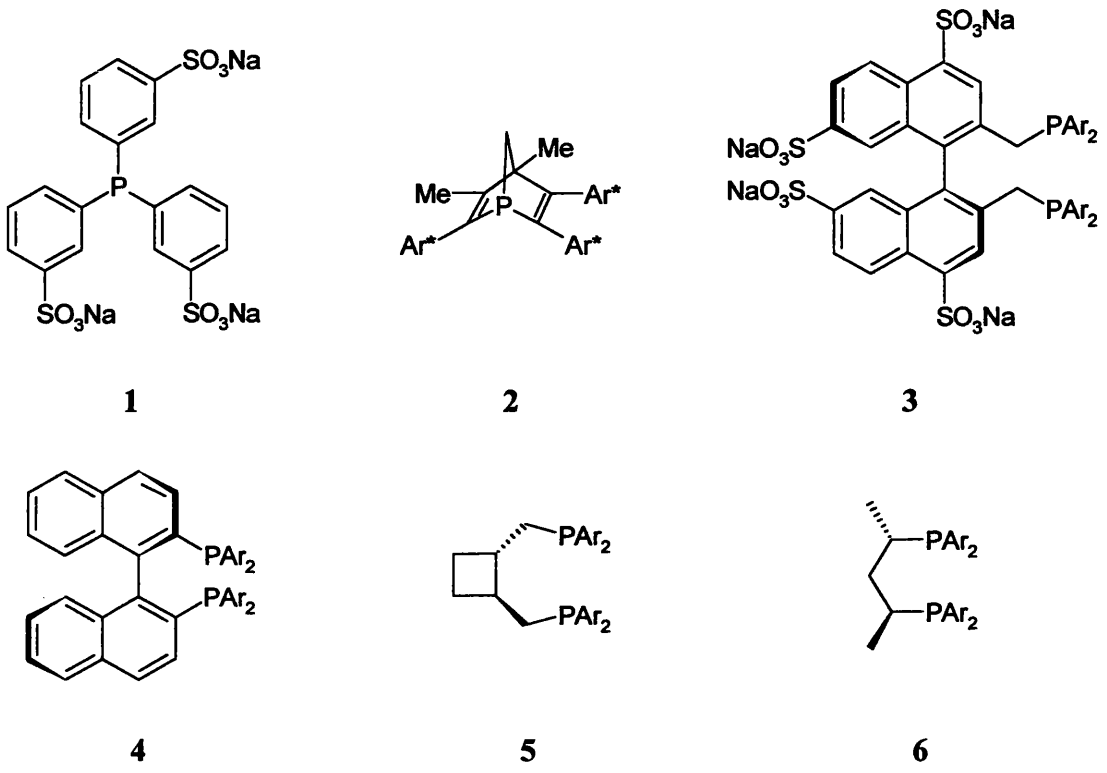
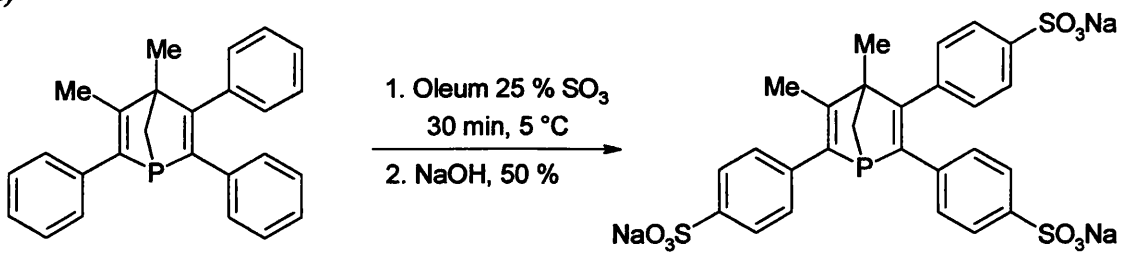


Figure 2. Water-soluble phosphines obtained by direct sulfonation.
(Ar* = *p*-$C_6H_4SO_3Na$, Ar = *m*-$C_6H_4SO_3Na$)

Water-soluble phosphines **1** – **6** were prepared by the direct sulfonation of the neutral 'mother phosphine' with oleum (SO_3 in concentrated H_2SO_4). Whilst this is the most successful procedure for the introduction of a sulfonate group, other methods have been investigated[10] because of problems associated with phosphine oxide formation, and with controlling the number and position of the sulfonate substituents (discussed further in section 2.2.1). One such method was used for the preparation of ligand **7** (Scheme 1); here the sulfonated alkyl side chain was introduced during the phosphine synthesis.

a)



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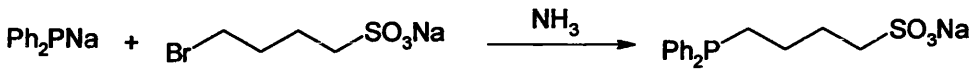
b)



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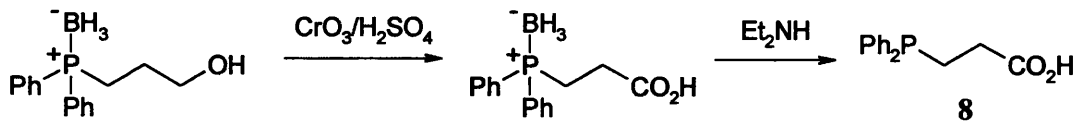
Scheme 1. Synthesis of sulfonated phosphines: a) Direct sulfonation, b) Introduction of the sulfonate group during phosphine synthesis.

Carboxylated Phosphines

Structures **8** – **12** are hydrophilic phosphines incorporating carboxylic acid functionalities. Whilst this group of water-soluble ligands was amongst the first to be studied, their application to aqueous catalysis has not been fully explored; much of the interest has centred on sulfonated phosphines whose water-solubility is somewhat greater. Mann *et al.* prepared the first example of a carboxylated phosphine **8,** in 1952 through the cyanoethylation reaction of acrylonitrile with diphenylphosphine and subsequent nitrile hydrolysis.[11] Pellon has also described a route to ligand **8** and related compounds, which utilises the oxidation of hydroxyalkylphosphine–borane complexes (Scheme 2).[12] A recent report demonstrates the use of such ligands in the rhodium catalysed hydrogenation of olefins under biphasic conditions.[13]



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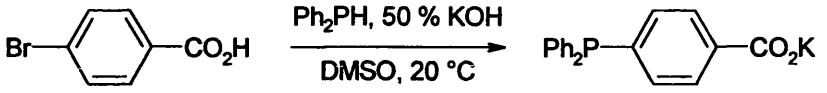
Scheme 2. Oxidation of hydroxyalkylphosphine–borane complexes as a route to carboxylated phosphines.

Phosphines of type **9** have been synthesised by the addition of *para-* or *meta-*bromobenzoic acid to a basic solution of diphenylphosphine (Scheme 3). A rhodium(I) complex of phosphine **9** demonstrated activity in the hydroformylation of oct-1-ene. The work-up procedure involved a series of extractions, which allowed isolation of the rhodium-phosphine species after reaction.[14]



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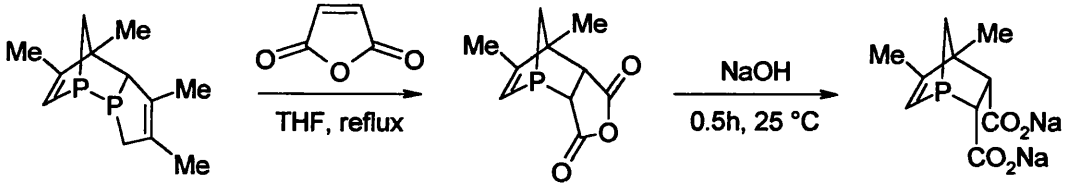
Scheme 3. A general synthesis for carboxylated phosphines.

Bicyclic phosphine **10** was obtained from the reaction of the [4+2] dimer[15] of 3,4-dimethyl-2*H*-phosphole with maleic anhydride in boiling THF, followed by hydrolysis with sodium hydroxide (Scheme 4).[16] Ligand **10** has a high water-solubility ($\geq$ 300 gdm^{-3}) and is structurally similar to established organic-soluble phosphine ligands;[17] however, its use for catalytic purposes has yet to be demonstrated.



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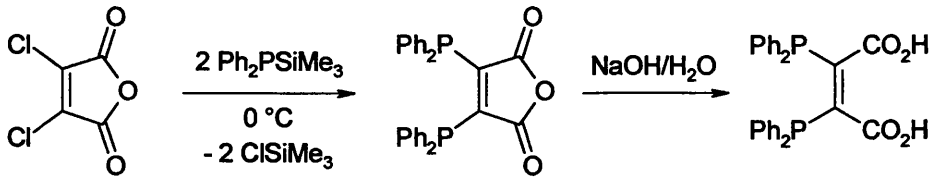
Scheme 4. Synthesis of a novel bicyclic carboxylated phosphine.

Tyler and co-workers[18] reported a synthetic route to the bidentate diphosphine **11** and also some examples of its tungsten and molybdenum complexes. The known ligand 2,3-bis(diphenylphosphino)maleic anhydride[19] was simply converted into ligand **11** using a solution of sodium hydroxide (Scheme 5).



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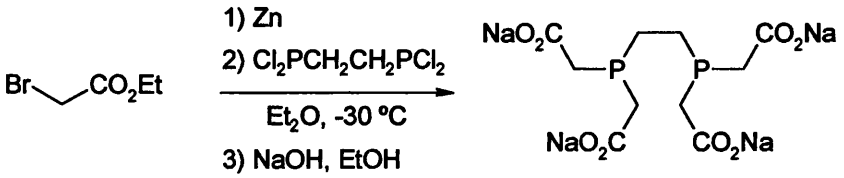
Scheme 5. Synthesis of a carboxylated bidentate diphosphine.

Podlahová and Podlaha prepared the phosphine analogue of ethylenediaminetetraacetic acid (tetrasodium salt) **12** via the alkylation of 1,2-bis(dichlorophosphino)ethane with excess Reformatsky reagent and hydrolysis of the intermediate ester (Scheme 6).[43]



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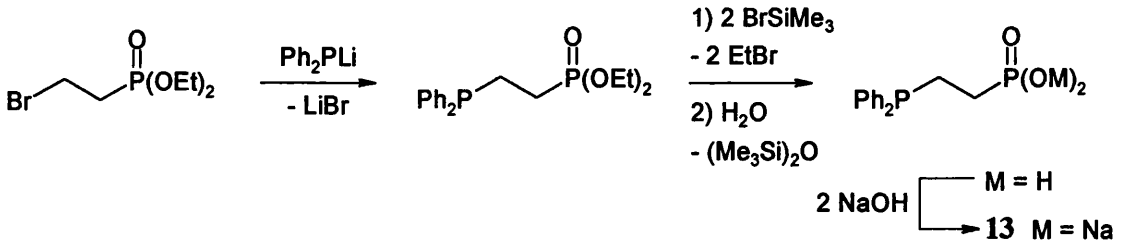
Scheme 6. Preparation of the phosphine analogue of EDTA.

Diphosphine **12** has been used along with other carboxyalkylphosphines for the extraction of transition metals from homogeneous reaction mixtures.[44]

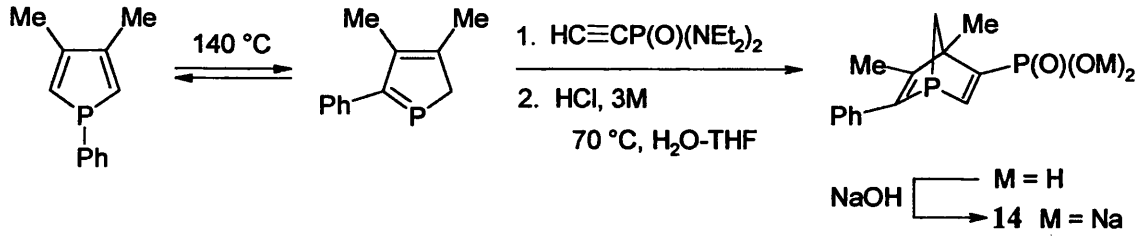
Phosphonated Phosphines

Phosphonate-functionalised phosphines constitute the smallest division of anionic phosphines. Roundhill and co-workers[10] prepared ligand **13** containing a phosphonated alkyl side chain (Scheme 7). Equimolar amounts of lithium diphenylphosphide and diethyl (2-bromoethyl)phosphonate were combined, and the intermediate diethyl ester converted into the bis(trimethyl)silyl ester. Hydrolysis of the silyl ester produced the free phosphonic acid, which after treatment with sodium hydroxide gave disodium salt **13**.



Scheme 7. Preparation of a phosphine containing an ethylphosphonate side chain.

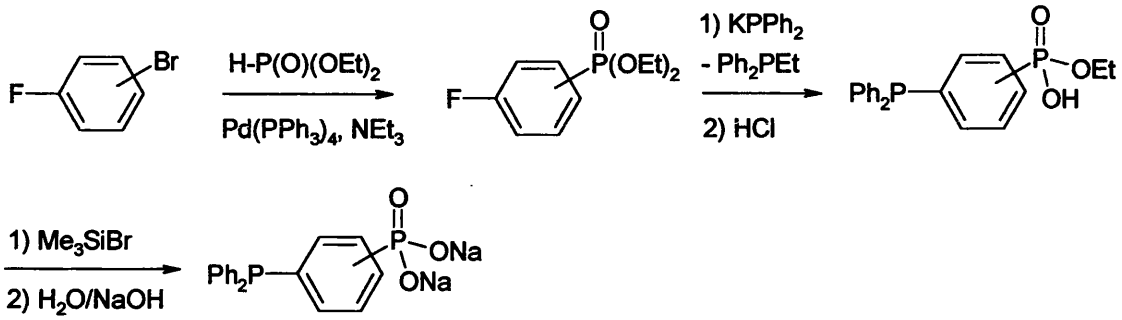
Following the success of the 'NORBOS' ligand in the biphasic hydroformylation of propene, Matthey and co-workers investigated the synthesis and use of phosphanorbornadienes functionalised with phosphonate groups. The reaction of 2-phenyl-3,4-dimethyl-5*H*-phosphole with ethynylphosphamide produced the phosphonamide derivative of ligand **14**. This was converted into the corresponding phosphonic acid by acid hydrolysis and finally into the highly soluble (230 gdm^{-3}) sodium salt **14** by treatment with sodium hydroxide (Scheme 8). Rhodium(I) complexes of this ligand were shown to be effective in the biphasic hydrogenation of 1-methylcyclohexene and also in the hydroformylation of 1-hexene.[20]



Scheme 8. Synthesis of a phosphanorbornadienephosphonate ligand.

Stelzer and co-workers[21] have recently reported a general synthesis of *meta*- and *para*-phosphonated aromatic phosphines of type **15** (Scheme 9). Palladium catalysed P–C coupling of *p*- or *m*-bromofluorobenzene with diethyl phosphite produced the required fluorophenylphosphonic ethyl ester, which was then subjected to nucleophilic phosphination with potassium diphenylphosphide. After acidification, transesterification and treatment with sodium hydroxide the phosphonated aromatic phosphine was isolated

as the disodium salt. Palladium(II) and platinum(II) complexes of the *para*-isomer of ligand **15** have been prepared.[22] The palladium complex of ligand **15** catalyses the carbonylation of benzyl chloride under biphasic conditions.



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Scheme 9. A general synthesis for phosphines with phosphonated aryl side chains.

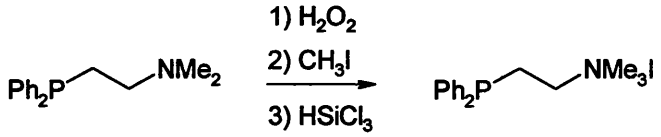
Cationic Phosphines: Included in this class are phosphines containing ammonium, phosphonium and guanidinium moieties.

Phosphines with Quaternised Aminoalkyl and Aminoaryl Groups

Water-soluble phosphines can be prepared by quaternisation of the nitrogen atom of aminoalkyl and aminoaryl phosphines. In most synthetic sequences, *N*-quaternisation takes place after the initial protection of the more reactive phosphorus centre, either by oxidation or by coordination to a metal. Subsequent reduction or decomplexation yields the desired phosphine. In contrast to the ligands previously discussed, phosphine ligands of this class should have a water-solubility that is independent of solution pH.

In 1982, Baird *et al.* reported the synthesis of AMPHOS iodide **16**, which was the prototype of cationic phosphines (Scheme 10). Protection of the phosphorus atom in the starting phosphine was achieved by oxidation with hydrogen peroxide. Alkylation at the nitrogen with methyl iodide, followed by reduction with trichlorosilane gave AMPHOS as the iodode salt.[23] Soon after the introduction of AMPHOS, rhodium(I) complexes

were developed for the hydrogenation and hydroformylation of various alkenes in water and aqueous biphasic systems.[24] More recently, a binuclear thiolato-bridged rhodium(I) complex has proved to be a highly active catalyst for the hydrogenation of unsaturated alcohols and acids.[25]



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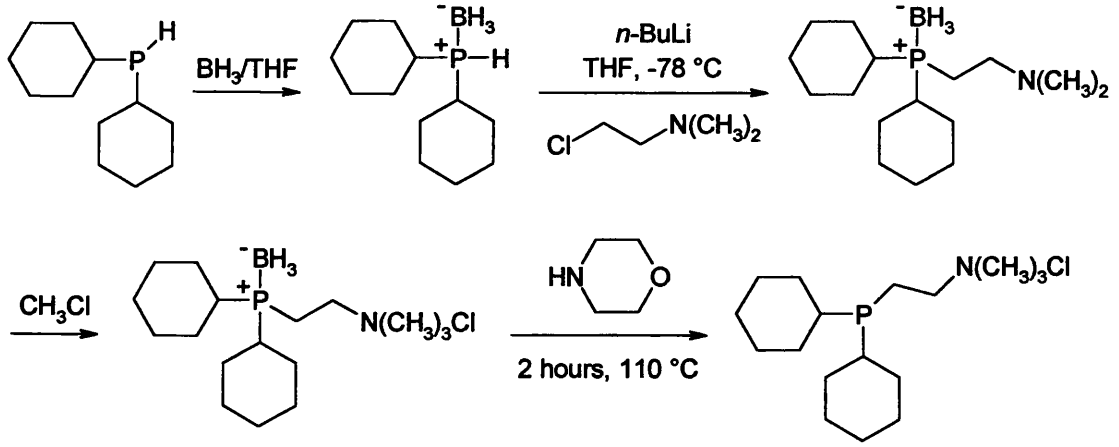
Scheme 10. Synthesis of AMPHOS iodide.

Grubbs and co-workers have developed a synthetic route to bulky, water-soluble, aliphatic phosphines[26] of type **17**, which utilises borane-protected phosphorus intermediates (Scheme 11). After initial phosphine protection, base assisted aminoalkylation generated the amine-functionalised phosphine-borane. Then, *N*-quaternisation with methyl chloride followed by *P*-deprotection with morpholine gave phosphine **17**. A ruthenium carbene complex incorporating ligand **17** demonstrated high activity in the ring opening metathesis polymerisation (ROMP) of 7-oxanorbornene derivatives in water, methanol and aqueous emulsions.



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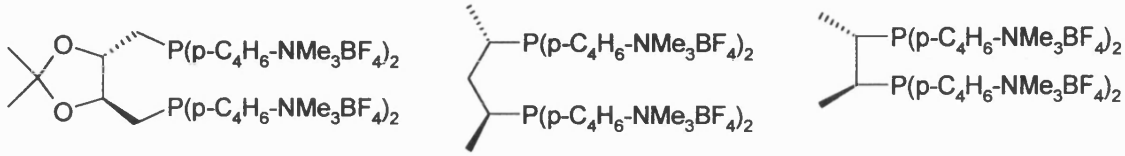
Scheme 11. Synthesis of an AMPHOS analogue via borane-protected intermediates.

There are few examples of chiral phosphines containing quaternised aminoalkyl or aminoaryl groups. Tóth and Hanson have prepared tetra-amine functionalised derivatives of the chiral diphosphines DIOP, BDPP and Chiraphos, which were *N*-quaternised after complexation with rhodium, thus providing the water-soluble rhodium complexes of ligands **18**, **19** and **20**.[27]



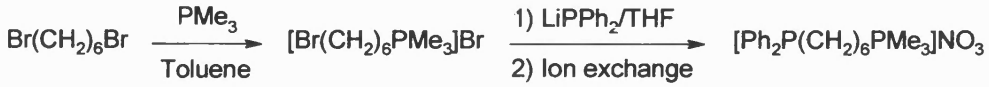
18 **19** **20**

(-)-(*S*,*S*)-DIOP-X_4 (-)-(*S*,*S*)-BDPP-X_4 (-)-(*S*,*S*)-Chiraphos-X_4

Figure 3. Chiral diphosphines with quaternised aminoaryl groups (X = NMe_3BF_4).

Phosphines with Terminal Phosphonium Groups

Baird and co-workers examined this relatively new class of water-soluble phosphine in 1991. Mono-quaternisation of bisphosphines yield phosphinoalkylphosphonium salts such as **21** (Scheme 12). Rhodium(I) complexes containing ligands of type **21** were shown to be highly active catalysts for the hydrogenation of *n*-hexene in aqueous biphasic systems.[28]



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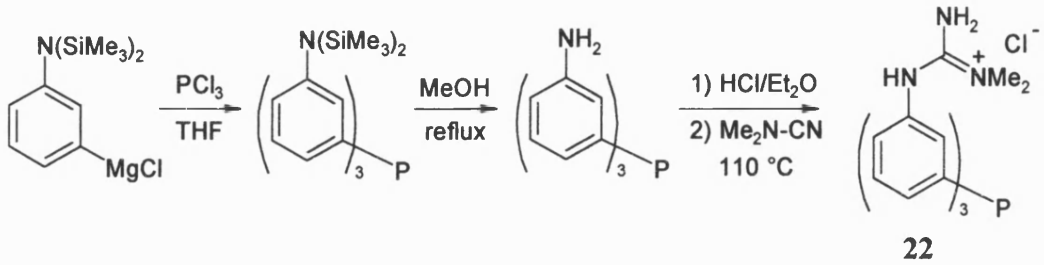
Scheme 12. Synthesis of phosphonium phosphines.

Phosphines with Guanidinium Moieties

Phosphines incorporating the extremely hydrophilic guanidinium group constitute a novel type of cationic ligand. Schmidtchen and co-workers developed the synthesis of **22** and related ligands. The introduction of the guanidinium group was achieved using

the well-established addition reaction of anilinium salts to cyanamides (Scheme 13).[29] More recently, Stelzer and co-workers have described a route to this class of ligand, which uses the palladium-catalysed P–C coupling reactions between iodophenyl guanidines and phenyl- or diphenylphosphine.[30] The use of guanidinium phosphines as ligands in the palladium-catalysed Castro-Stephens coupling of iodobenzoate and *N*-(trifluoroacetyl)propargylamine in aqueous solution proved to be successful.



22

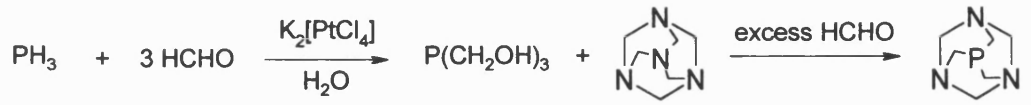
Scheme 13. Synthesis of a phosphine containing cationic guanidinium phenyl moieties.

Non-ionic Phosphines: In this class are phosphines carrying hydroxylic and polyether substituents.

Phosphines with Hydroxylic Substituents

Attainment of water-solubility through the incorporation of hydroxylic groups into the ligand periphery has attracted some attention. Enhanced solubility is often not exhibited unless the phosphine carries several hydroxylic substituents. A large-scale synthesis of ligand **23** is based on the platinum-catalysed addition of PH_3 to aqueous formaldehyde (Scheme 14).[31] Initial investigations into transition metal complexes of phosphine **23** were carried out by Chatt and co-workers.[32] More recently, the ruthenium complex [Cp*Ru(CO)Cl(**23**)] has been used for the hydrogenation of sorbic acid in a biphasic water-heptane mixture.[33] Tris(hydroxymethyl)phosphine **23** also plays a role as a precursor in the synthesis of triaza-7-phosphaadamantane **24**, another relatively

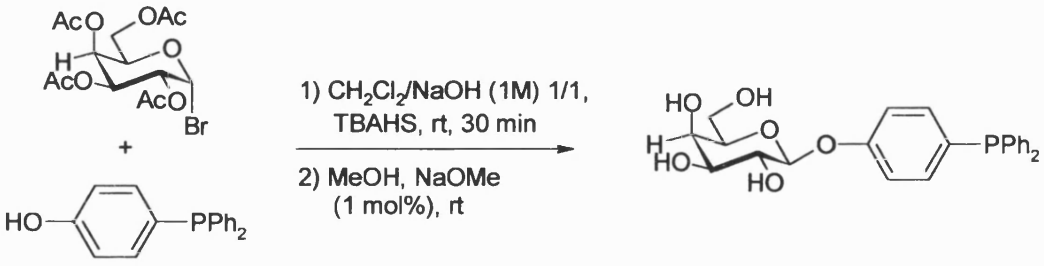
important non-ionic phosphine ligand. The ruthenium(II) complex $RuCl_2(\mathbf{24})_4$ is an effective catalyst for the conversion of aldehydes into alcohols in aqueous biphasic systems.[34]



23 **24**

Scheme 14. Non-ionic monophosphine ligands.

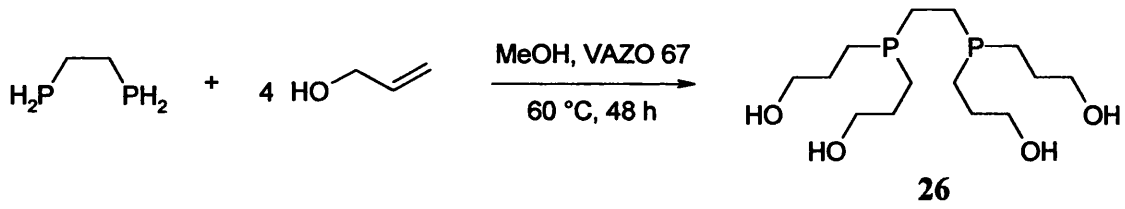
Hydrophilic hydroxyalkylphosphines containing carbohydrate moieties have also been reported.[35] Beller and co-workers prepared ligands of type **25** via two-phase glycosidation of *p*-hydroxyphenyldiphenylphosphine with acetyl-protected halopyranoses and subsequent acetyl cleavage (Scheme 15). The palladium complex obtained from sugar phosphine **25** and $Pd(OAc)_2$ demonstrated a higher catalytic activity in biphasic Suzuki and Heck coupling reactions than the corresponding palladium-TPPTS complex.



25

Scheme 15. Preparation of a phosphine containing a galactose moiety.

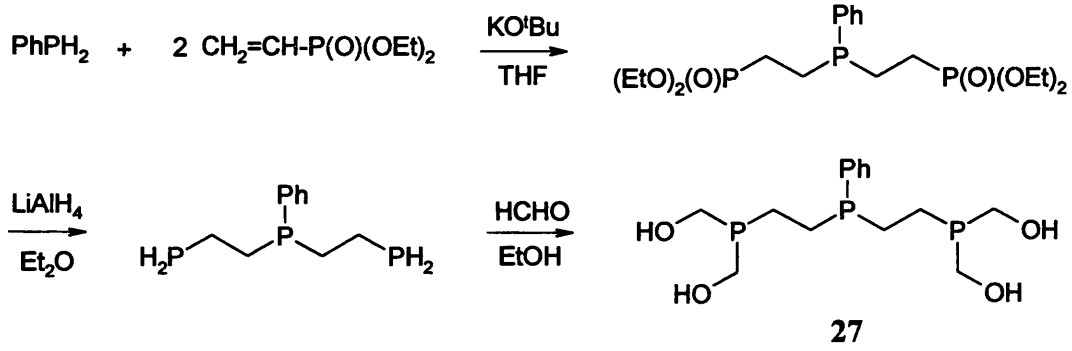
Tyler and co-workers have recently synthesised the chelating diphosphine **26** by the free radical addition of allyl alcohol to 1,2-bis(phosphino)ethane (Scheme 16). Rhodium(I) complexes of ligand **26** were shown to be effective in the biphasic hydrogenation of hexene.[36]



26

Scheme 16. Synthesis of a hydroxylated diphosphine under free-radical conditions (VASO 67 = 2,2'-azobis(*iso*-butyronitrile)).

Katti *et al.* were interested in the co-ordination chemistry of tripodal phosphines. During their research they developed a three-step synthesis of the unique water-soluble triphosphine **27**, which consisted of the Michael-type addition of phenylphosphine with diethyl vinylphosphonate, reduction of the diphosphonate intermediate, and finally formylation of the phosphine precursor to yield triphosphine **27** (Scheme 17).[37]

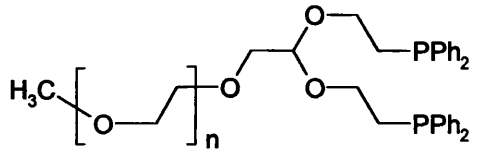


27

Scheme 17. Synthesis of a hydroxylated triphosphine.

Phosphines with Polyether Substituents

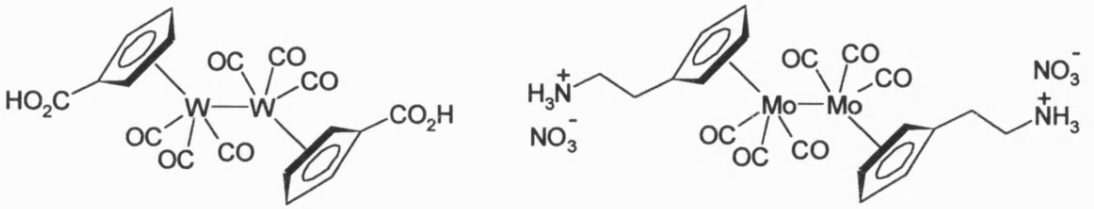
The water-solubility of polyether-substituted phosphines is dependent on the length of the polyether chain;[2] for example, ligands of the type **28** are only water-soluble when $n >$ 15. Phosphines of this class have predominantly been used for hydroformylation reactions under thermoregulated phase-transfer conditions.[38]



28

1.1.3.2 Non-Phosphines

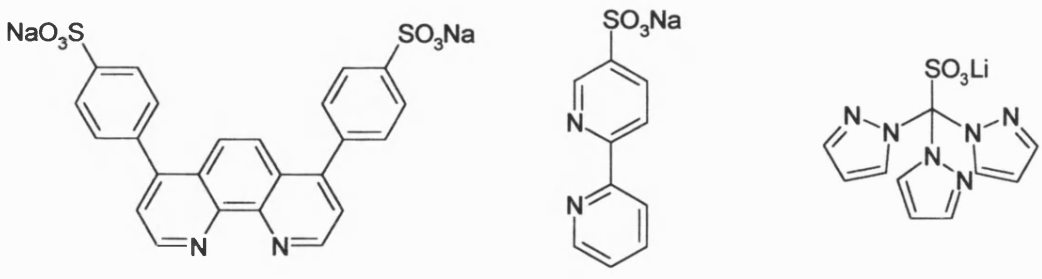
Research in the area of aqueous catalysis has been dominated by the synthesis and application of phosphine-based ligands. However, a number of non-phosphine ligands have been reported. Tyler and co-workers have developed water-soluble tungsten and molybdenum carbonyl dimers **29** and **30** (Figure 4) containing functionalised cyclopentadienyl-based ligands; these were used as precursors in the generation of 19-electron complexes in aqueous media.[39]



29 **30**

Figure 4. Metal complexes solubilised by functionalised cyclopentadienyl ligands.

Nitrogen donor ligands containing sulfonate functionalities can also be found in the literature. These include sulfonated analogues of phenanthroline[40] **31**, 2,2'-bipyridine[41] **32** and tris(pyrazolyl)methane[42] **33** (Figure 5). Also, Section 2.2.2 describes the synthesis of sulfonated aminosulfonamide ligands; these represent a new class of enantiomerically pure, water-soluble, non-phosphine ligand.



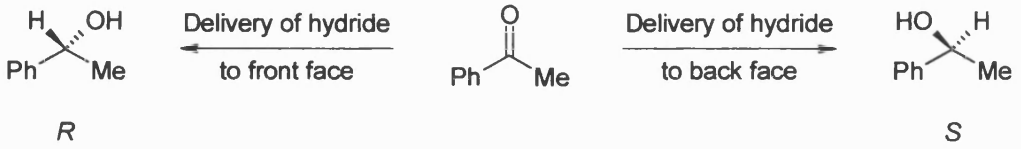
31 **32** **33**

Figure 5. Water-soluble nitrogen-donor ligands.

1.2 Asymmetric Transfer Hydrogenation

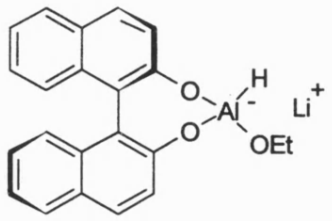
1.2.1 Enantioselective Reduction of Ketones[45]

The asymmetric reduction of ketones is a widely studied and synthetically important reaction. The enantiomerically enriched secondary alcohols produced by such a process are useful building blocks for organic synthesis or may be valuable products in their own right. In fact, the most commonly found asymmetric centres are those bearing alcohol functionalities.

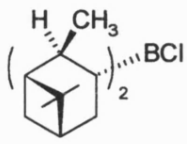


Scheme 18. Asymmetric reduction of acetophenone.

The asymmetric reduction involves the delivery of hydride selectively to one face of the substrate (Scheme 18). Standard stoichiometric reducing agents such as lithium aluminium hydride,[46] sodium borohydride and borane[47] have been modified with enantiomerically pure ligands in order to achieve this objective (Figure 6). It is believed that these reagents transfer hydride to each face of the ketone through two diastereomerically distinct transition states. As these will have differing energies, the reaction will preferentially proceed via the lower energy transition state, therefore producing an excess of one enantiomer of product (Figure 7).

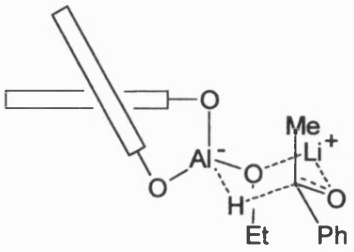


(*R*)-BINAL-H

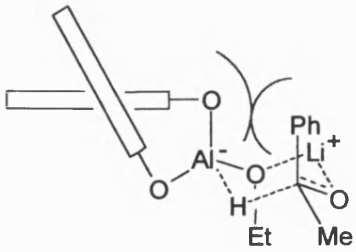


Chlorodiisopinocampheylborane

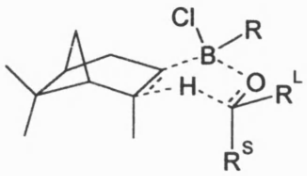
Figure 6. Stoichiometric reagents for asymmetric reduction.



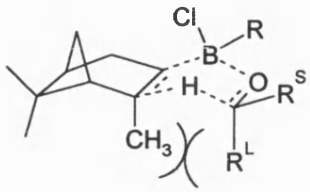
Favoured – low energy



Disfavoured – high energy



Favoured – low energy



Disfavoured – high energy

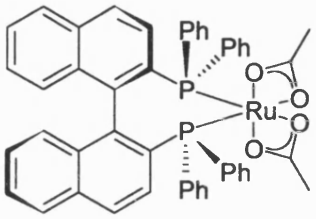
Figure 7. Proposed diastereomeric transition states (R^L = large group, R^S = small group, R = isopinocampheyl).

Whilst these reagents have produced some impressive results, they suffer one major disadvantage; that is, they are stoichiometric reagents. Therefore, at least one mole of reagent is required to reduce one mole of ketone. On a large-scale, the use of such reagents would be unfeasible due to their high costs and handling requirements. A far more attractive system employs an enantiomerically pure catalyst along with stoichiometric amounts of achiral reducing agent. Of course, a system such as this requires that the substrate and reducing agent must not react in the absence of the catalyst. The reaction in which the new asymmetric centre is formed occurs only when the catalyst brings together the reducing agent and substrate. As the catalyst is enantiomerically pure, it follows that the transition states in which it is involved will be diastereomeric; therefore, similar arguments to those already discussed may be used to explain the origin of the asymmetric induction.[48]

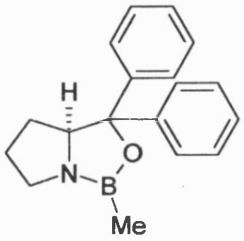
Naturally occurring catalysts are available for the asymmetric reduction of ketones in the form of enzymes. Often, the enzyme functions inside a whole cell such as a yeast. Of

these, Baker's yeast (*Saccharomyces cervisiae*) has proved to be a popular choice and has been used successfully in the reduction variety of substrates.[49]

Many chemists have endeavoured to develop synthetic catalysts, which are able to mimic the action of enzymes whilst being far less complex. There are several examples of such reagents, which include the ruthenium-BINAP complex **34** introduced by Noyori[50] and the oxazaborolidine catalysts (e.g. structure **35**) developed by Corey (Figure 8).[51]



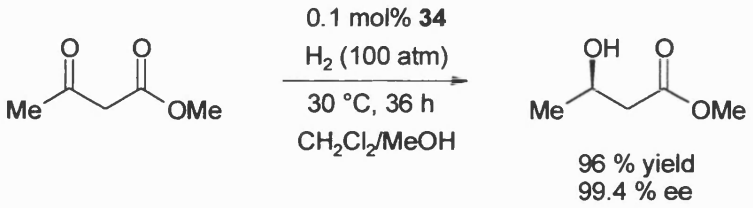
34



35

Figure 8. Catalysts for asymmetric hydrogenation.

Catalyst **34** has proven to be highly enantioselective in the hydrogenation of ketones when there is a suitable co-ordinating group adjacent to the keto-group (Scheme 19). The reduction then proceeds in a well-defined asymmetric environment centred on the ruthenium atom. As hydrogen is the stoichiometric reductant the reaction generates no by-products.



Scheme 19. Reduction of β-keto esters.

Perhaps the most significant reduction catalysts are those of type **35**. The oxazaborolidine structure incorporates neighbouring acceptor (boron) and donor

(nitrogen) atoms, which act as docking sites for the ketone substrate and borane reducing agent. It is assumed that the ketone interacts with the Lewis acidic boron atom through the oxygen lone pair that is *trans* to the larger substituent (i.e. the phenyl group for acetophenone). Then, delivery of hydride may take place via the six membered transition states shown in Figure 9. The second transition state is however, disfavoured owing to the strong steric interaction between the methyl group of the substrate and the phenyl substituent of the catalyst.

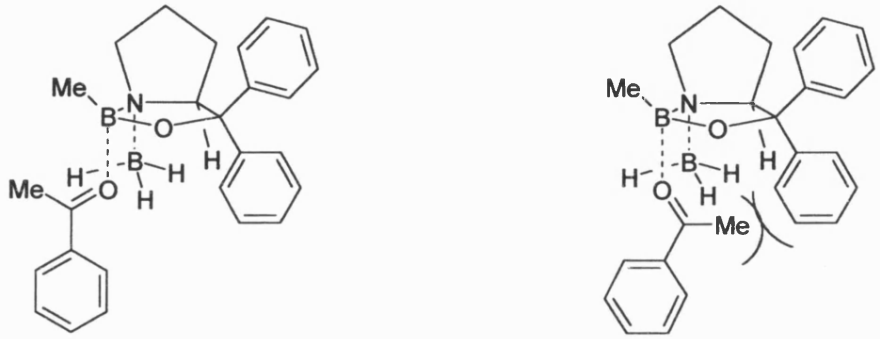
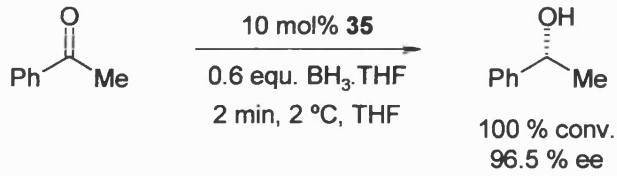


Figure 9. Proposed diastereomeric transition states for oxazaborolidine catalysts.

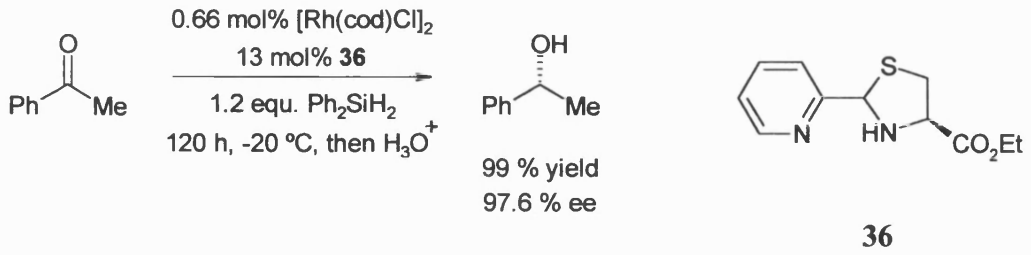
Whilst the oxazaborolidine system has proved extremely effective (scheme 20) it does have some disadvantages; namely, the high catalyst loading (typically 10 mol%) often required, and also the sensitivity of borane to water and some functional groups.



Scheme 20. Reduction of acetophenone using an oxazaborolidine catalyst.

An additional technique for the catalytic asymmetric reduction of ketones that should be mentioned is asymmetric hydrosilylation (Scheme 21). Here, the ketone substrate is first

converted into the silyl ether, which is then hydrolysed into the corresponding alcohol. Rhodium catalysts containing enantiomerically pure nitrogen-based ligands (e.g. ligand **36**) have attracted the most attention.[52]

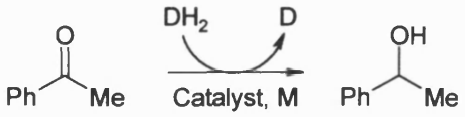


36

Scheme 21. Asymmetric hydrosilylation.

1.2.2 Transfer Hydrogenation[53]

For many years, the oxazaborolidine and ruthenium-BINAP catalysts dominated the area of enantioselective ketone reduction, with asymmetric transfer hydrogenation catalysts remaining underdeveloped. However, major advances have been made in this field recently. The discovery of particularly active and highly enantioselective catalysts has made transfer hydrogenation a realistic alternative to the reduction procedures discussed previously.



Scheme 22. Transfer hydrogenation (DH_2 = hydrogen donor).

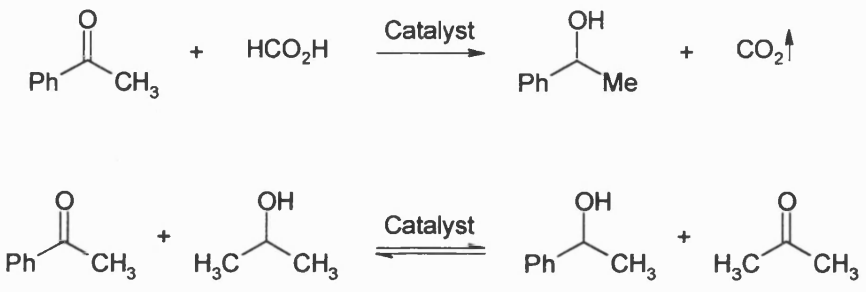
Transfer hydrogenation is defined as 'the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst', as depicted in Scheme 22. The main advantage of this method stems from the hydrogen donor, which is usually a small organic molecule such as 2-propanol or formic acid. These inexpensive reagents are easily handled and stored, thereby eliminating the need for specialised equipment; this is in contrast to those hydride sources previously mentioned (e.g. molecular hydrogen,

borane). Therefore, the operational simplicity of transfer hydrogenation makes it an attractive process for use in small to medium scale reactions.

1.2.2.1 Hydrogen Donors

Conceptually, a hydrogen donor (DH_2) is any molecule that is capable of giving up hydrogen. The donors most commonly used for the transfer hydrogenation of ketones are 2-propanol and formic acid (usually used as the triethylamine azeotrope[54]). The latter allows the reaction to proceed irreversibly, since the dehydrogenated product of formic acid is carbon dioxide gas. If 2-propanol is employed as the hydrogen donor an equilibrium exists, the position of which depends upon the structure of the ketone substrate and on the reaction conditions (Scheme 23). Often, the reduction process is thermodynamically unfavourable and the position of equilibrium is to the left. Therefore, an excess of 2-propanol is required in order to produce respectable conversions. In fact, the majority of transfer hydrogenation reactions are performed with the hydrogen donor as the solvent. The position of equilibrium may also be shifted of course, by removing acetone from the reaction mixture, but this is technically difficult.

Using the respective electrode potentials[55] of acetophenone and acetone, it is possible to calculate the ratio of 1-phenylethanol:acetophenone at equilibrium. Thus, it was determined that 0.1, 1.0 and 2.0 M solutions of acetophenone in 2-propanol would give equilibrium ratios of 98:2, 80:20 and 70:30 respectively.[56]



Scheme 23. Formic acid and 2-propanol as hydrogen donors.

The reversible nature of the reaction not only limits the amount of alcohol product obtainable but also causes erosion of enantiomeric purity. This effect results from the different rates at which the enantiomers of product undergo the reverse reaction (dehydrogenative oxidation). The major enantiomer will react relatively quickly since the reaction pathway has a lower energy transition state; on the other hand, the minor enantiomer will react more slowly via a transition state of higher energy. Therefore, even if the forward reaction proceeds with exceptional enantioselectivity, the presence of the reverse process will gradually reduce the enantiomeric excess. The impact of the reverse reaction can however, be minimised by avoiding an unnecessarily long exposure of the catalyst to the reaction mixture. That is, the reaction should be terminated as soon as equilibrium has been reached.

1.2.2.2 Reaction Mechanism

The precise mechanism operating in the transfer reduction system depends on the metal catalyst and the hydrogen donor. Three distinct mechanisms have been described: (a) direct hydrogen transfer; (b) the hydridic route; and (c) the metal – ligand bifunctional mechanism.

Direct hydrogen transfer proceeds via a mechanism similar to that proposed for the Meerwein-Ponndorf-Verley (MPV) reduction.[55(b),57] This is a concerted process, involving a six-membered cyclic transition state in which the metal complex assembles the hydrogen donor (2-propanol) and hydrogen acceptor (ketone) in the appropriate orientation (Figure 10). This is reportedly the preferred mechanism of reduction when lanthanide[58] and main group metals are involved.

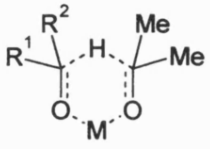
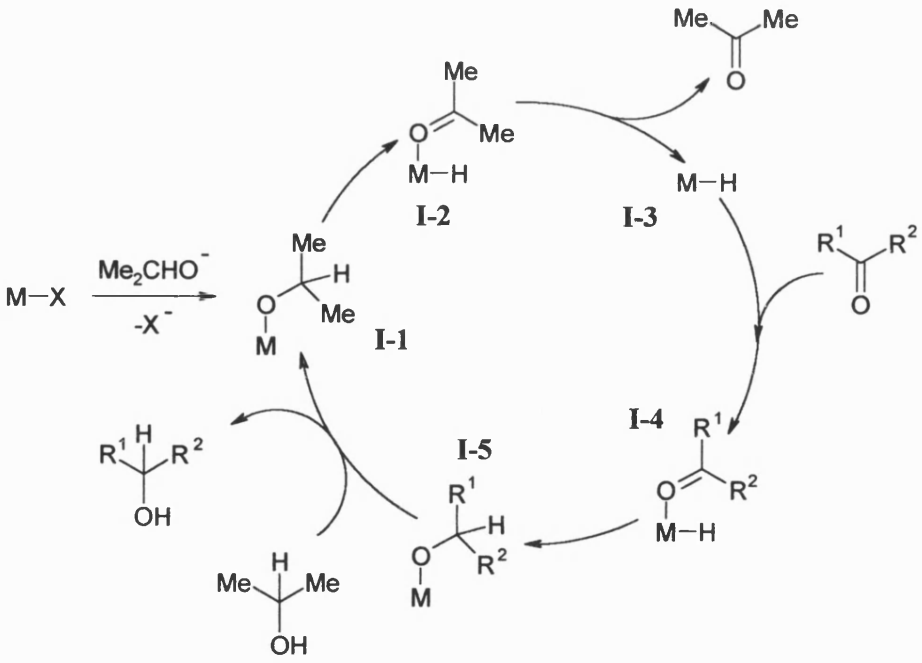


Figure 10. MPV-type transition state (e.g. M = Sm).

If the transfer reduction is undertaken using transition metals bearing tertiary phosphine or sp^2-hybridised amine ligands, then the hydridic route is the generally accepted reaction mechanism. Most reactions are promoted by the presence of a catalytic amount of base, which is believed to increase the concentration of the 2-propoxide anion in the system, thereby facilitating the reaction.[59]

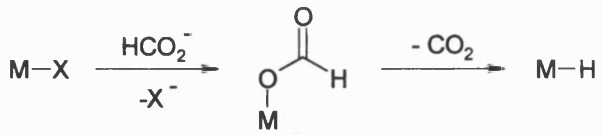
The first step in the mechanism is the displacement of X from the catalyst precursor MX (X is typically halide, e.g. chloride, supporting ligands omitted) by 2-propoxide to form the transition metal 2-propoxide **I-1**. Elimination of acetone from intermediate **I-1** via complex **I-2** forms metal hydride **I-3**. Subsequent migratory insertion of the carbonyl group of the substrate into the metal-hydride bond occurs via complex **I-4**, resulting in metal alkoxide **I-5**. Finally, ligand exchange between intermediate **I-5** and 2-propanol completes the catalytic cycle (Scheme 24).[60]



Scheme 24. Transfer reduction – hydridic route (M = transition metal, X = anionic ligand).

A similar mechanism to that above would be expected when using formic acid/triethylamine azeotrope as a hydrogen donor. Reaction of this activated form of

formic acid[54] with the catalyst precursor provides the metal hydride species; carbon dioxide gas is eliminated during the process (Scheme 25).



Scheme 25. Transition metal hydride formation using activated formic acid.

Noyori has recently proposed a third mechanism for the transfer reduction of ketones by Ru(II) arene complexes with bidentate β-amino alcohol[61] or tosylated diamine ligands.[62] The metal-ligand bifunctional mechanism[60] involves the concerted transfer of hydride and a proton to the ketone substrate via a six-membered cyclic transition state (Figure 11). This mechanism will be discussed in greater detail in Section 2.3.1

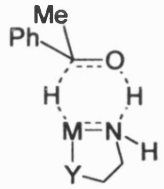


Figure 11. Proposed transition state for the metal-ligand bifunctional mechanism (M = Ru, Y = NTs, O).

1.2.2.3 Ligands and Catalysts

Numerous ligands have been reported for the enantioselective transfer reduction of ketones, usually in combination with either ruthenium, rhodium or iridium metals. Unlike asymmetric hydrogenation, the most successful catalysts in the area of enantioselective transfer reduction contain ligands with nitrogen rather than phosphorus donor atoms. The various ligands that have been employed have been reviewed in detail recently;[53b] the discussion here will concentrate only on the most effective (Figure 12). Table 1 compares the yield/conversion and enantiomeric excess obtained with each ligand in the transfer reduction of acetophenone into 1-phenylethanol.

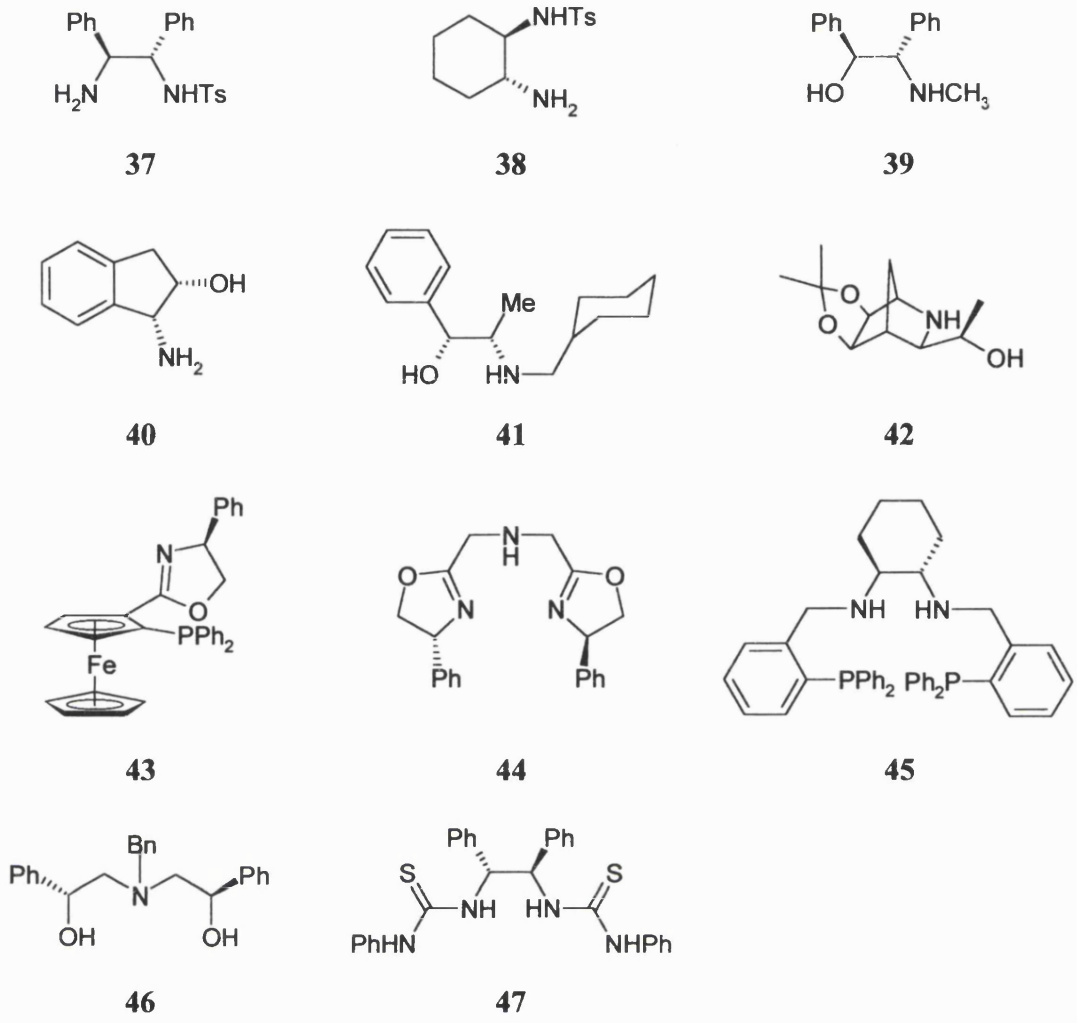


Figure 12. Ligands used in the asymmetric transfer hydrogenation of acetophenone.

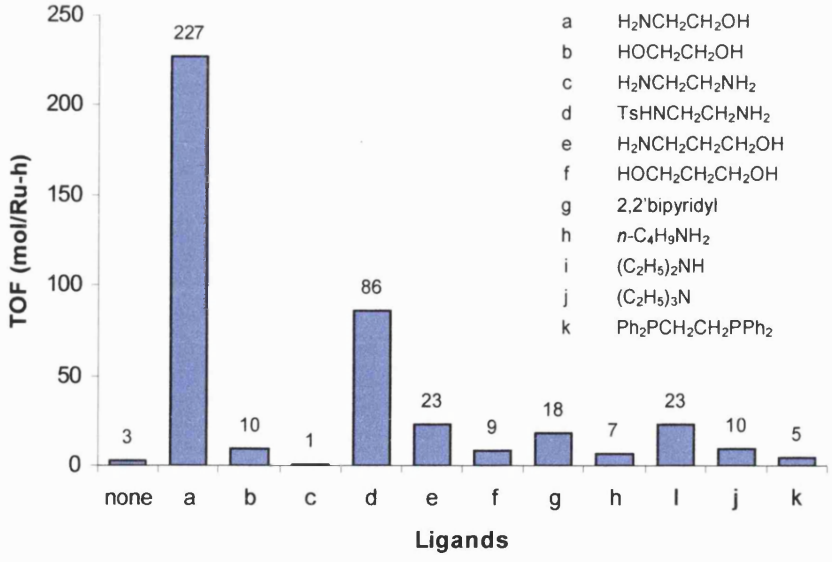
Ligand	Metal	Time (h)	Temp. (°C)	Yield/Conv. (%)	ee (%)	Ref.
37	**Ru(II)**	**15 (20)**	**rt (28)**	**95 (99)**	**97 (98)**	**62a (62i)**
37	Rh(III)	48	rt	80	90	62b
37	Ir(III)	48	rt	58	90	62b
38	Ru(II)	24	22 (30)	97 (99)	89 (94)	62d
38	Rh(III)	12	30	85	97	62e
38	Ir(III)	12	30	36	96	62e
39	Ru(II)	1	28	94	92	61a
40	Ru(II)	1.5	rt	70	91	61c
41	Ru(II)	6	10	91	95	61d
42	**Ru(II)**	**0.10**	**rt**	**96**	**96**	**61e**
43	Ru(II)	6	rt	93	94	63
44	Ru(II)	0.17	82	91	97	64
45	Ru(II)	7	45	93	97	65
46	Sm(III)	2	rt	74	96	58
47	Ru(II)	9	82	98	87	66

* Values in parentheses refer to experiments using a formic acid/triethylamine azeotrope hydrogen donor.

Table 1. Asymmetric transfer hydrogenation of acetophenone (hydride source – 2-propanol)*.

Undoubtedly, the introduction of mono-tosylated 1,2-diamine[62] and β-amino alcohol[61] ligands has been the most important development in the area of enantioselective transfer hydrogenation. The research in this field has been led by Noyori whose pioneering work has produced ligand **37**, which is perhaps the most outstanding ligand yet reported. Also, Andersson and co-workers have made major contributions towards the development of β-amino alcohol ligands. Their latest communication describes the synthesis and use of β-amino alcohol **42**, which is another example of a truly exceptional ligand.[61e]

Initial research undertaken by Noyori examined the influence of various ligands on the rate of reduction of acetophenone in a solution of 2-propanol containing $[RuCl_2(\eta^6\text{-benzene})]_2$ and potassium hydroxide. Whereas a reaction system containing no added ligand proved to be almost inert at room temperature, certain non-phosphine based ligands were found to have an accelerative effect on the reduction process. The observed turnover frequency (TOF, moles of 1-phenylethanol produced per mole of Ru per hour) during the first 20 minutes of reaction at a temperature of 28 °C is given in Graph 1.[56]



Graph 1. Ligand acceleration effects on the transfer hydrogenation of acetophenone.

The results of the screening experiments indicated that ethanolamine afforded the highest level of rate enhancement (a 75 fold increase over the background rate), which naturally led to the use of *β*-amino alcohols such as ligands **39** – **42** for asymmetric catalysis.[61] Of these, 2-azanorbornyl derivative **42** is the most recent and most exceptional *β*-amino alcohol ligand to be reported.[61e] It was produced by the careful modification of (1*S*,3*R*,4*R*)-2-azanorbornylmethanol, which is a successful ligand in its own right.[61b] The combination of ligand **42** and $[RuCl_2(p\text{-cymene})]_2$ effects highly enantioselective transfer hydrogenation at low catalyst loadings and high rate. Acetophenone was reduced in 96 % ee with a substrate to catalyst ratio (S/C) of 5000 (0.01 mol% $[RuCl_2(p\text{-cymene})]_2$) within 90 minutes!

Mono-tosylated ethylenediamine gave the second-highest level of rate increase (a 30 fold increase over the background rate), and as a consequence of this, asymmetric ligands **37** and **38** were developed.[62]

Additional experiments by Noyori demonstrated that the presence of a primary or secondary amine functionality within the ligand is essential for catalytic activity; dimethylamino analogues proved to be totally ineffective. The choice of ancillary ligand is also important. Four aromatic ligands with varying electronic and steric properties were examined. Complexes of benzene demonstrated the highest activity but the lowest enantioselection. Mesitylene and *p*-cymene complexes were relatively active and highly enantioselective, whilst catalysts incorporating hexamethylbenzene exhibited the lowest activity. Extensive computer modeling studies[60,67] along with experimental observations have allowed a good understanding of the mode of operation of both mono-tosylated diamine and *β*-amino alcohol ligands in ruthenium-catalysed hydrogen transfer. Further discussion of ligands **37** and **38** can be found in Section 2.3.

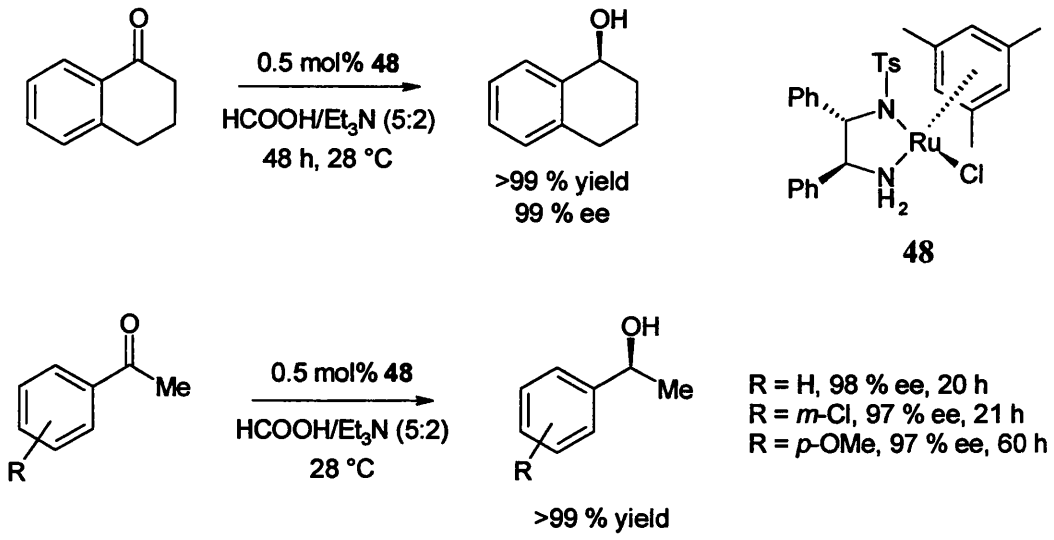
Notable amongst the many other ligands reported for ruthenium-catalysed asymmetric transfer hydrogenation are oxazoline-based ligands **43**[63] and **44**,[64] tetradentate

diamine/diphosphine **45**[65] and thiourea **47**.[66] Tridentate ligand **46** has been has been utilised in the formation of an enantiomerically pure samarium(III) complex. The effective use of this in Meerwein-Ponndorf-Verley type reductions has been described by Evans.[58]

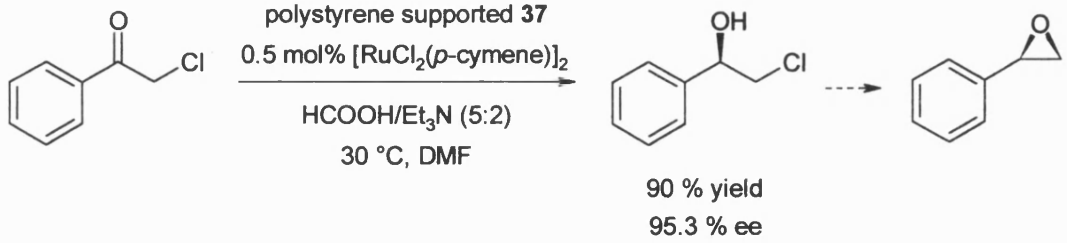
Without doubt, nitrogenous ligands have surpassed phosphine ligands in this area of asymmetric catalysis, and since the chemistry of nitrogen-based organic compounds is relatively rich, the synthesis and evaluation of new ligands should continue for some time.

1.2.2.4 Substrates (Hydrogen Acceptors)

The vast majority of enantioselective hydrogen transfer reactions has concerned the reduction of simple aryl alkyl ketones, including various acetophenones and cyclic ketones (Scheme 26a).[62i] Substituted acetophenones are particularly useful substrates for asymmetric reduction because the alcohol products may be converted into valuable synthetic intermediates. For example, the alcohol resulting from the reduction of 2-choloroacetophenone (i.e. 2-chloro-1-phenethanol) can be converted into the corresponding epoxide (Scheme 26b).[69]

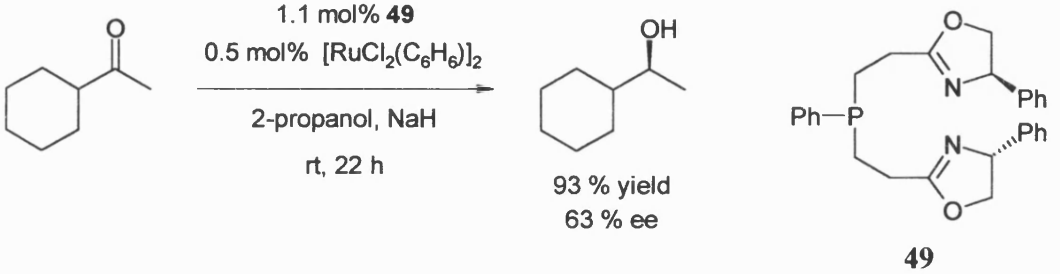


Scheme 26a. Aryl alkyl ketones as hydrogen acceptors.



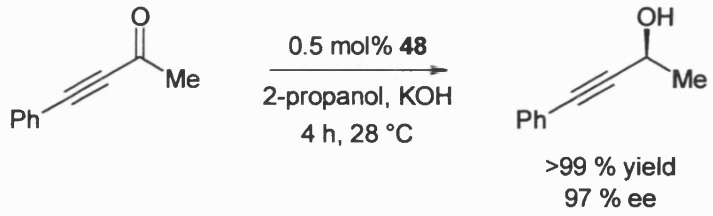
Scheme 26b. Aryl alkyl ketones as hydrogen acceptors.

Reductions involving alkyl alkyl ketones such as cyclohexyl methyl ketone[68] generally proceed with lower selectivity (Scheme 27). Aryl aryl ketones (e.g. benzophenones) are seldom used as substrates.



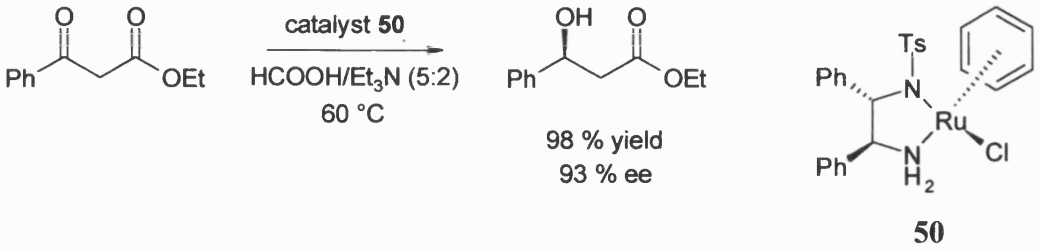
Scheme 27. Alkyl alkyl ketones as hydrogen acceptors.

The asymmetric transfer reduction of acetylenic ketones provides a highly effective and convenient route to enantiomerically enriched propargylic alcohols. These compounds are considered to be valuable building blocks for the synthesis of various biologically active and structurally interesting compounds (Scheme 28).[62h]



Scheme 28. Synthesis of enantiomerically enriched propargylic alcohols.

Tosylated diamine **37** has also been utilised in the reduction of keto esters. Accordingly, the enantioselective synthesis of α-, β- and δ-hydroxy esters was realised (Scheme 29).[56]



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Scheme 29. Asymmetric transfer reduction of β-keto esters.

1.3 Biphasic and Supported Aqueous Phase Catalysis

1.3.1 Introduction[1,70]

For industrial use, it is necessary for a catalyst to possess high activity along with high regio- and stereoselectivity. Indeed, these desirable properties have been attained through the development of homogeneous transition metal catalysis over several decades.[71] Yet despite such advancements, homogeneous catalysts have been underused in the chemical industry principally because of the problematic separation of the dissolved catalyst from the reaction products. Efficient separation is especially required when the reaction products are to be used in the manufacture of drugs, since there is a toxicity associated with transition metal residues. At present, it is estimated that 80 % of catalytic reactions used in industry still employ heterogeneous catalysts, whilst only 20 % involve homogeneous catalysts.

Thus, a great deal of research has concentrated on producing a catalytic system in which the favourable characteristics of both homogeneous and heterogeneous systems are combined. That is, a system containing a catalyst which is highly active and selective whilst also being easy to separate from the reaction products. Many of the methods for the 'heterogenisation' of homogeneous catalysts have focused upon anchoring the ligands of the transition metal catalyst to various solid supports. However, this technique has often lacked success. The efficacy of the modified catalyst is often suppressed because of its restricted mobility, which results from the anchoring process. A somewhat more successful mode of immobilsation employs a 'liquid support'. Here, two immiscible liquid phases are utilised, one containing the catalyst and the other containing the reactants and ultimately the products. The potential of this biphasic catalysis continues to increase, as new water-soluble organometallic catalyst complexes are introduced.

Recently, an additional technique has been described to bridge the gap between homogeneous and heterogeneous catalysis. Supported aqueous phase (SAP) catalysis combines a biphasic catalytic system with a solid support. A hybrid system such as this may hold several advantages over the biphasic system alone; these include a possible improvement in reaction rate and selectivity. The following discussion gives a more detailed account of homogeneous and heterogeneous catalysis, and the subsequent sections examine biphasic and supported liquid phase catalysis as 'heterogenisation' techniques.

1.3.2 Homogeneous versus Heterogeneous Catalysis

Homogeneous catalytic systems contain both reactants and catalyst in a common liquid phase. The catalyst is usually a single, well defined transition metal complex. In heterogeneous systems, the catalyst is typically present as a solid and the reactants as liquids or, more frequently gases. Reaction then takes place at the phase interface, that is, on the surface of the catalyst. Table 2 compares the major aspects of homogeneous and heterogeneous catalysis.

	Homogeneous catalysis	Heterogeneous catalysis
Activity (relative to metal content)	High	Variable
Selectivity	High	Variable
Reaction conditions	Mild	Harsh
Service life of catalyst	Variable	Long
Sensitivity towards catalyst poisons	Low	High
Diffusion problems	None	May be important
Catalyst recycling	Expensive	Not necessary
Variability of steric and electronic properties of catalysts	Possible	Not possible
Mechanistic understanding	Possible	More or less impossible

Table 2. Homogeneous versus heterogeneous catalysis.

	Homogeneous catalysis	Heterogeneous catalysis	
		Suspension	Fixed bed
Separation	Filtration after chemical decomposition Distillation Extraction	Filtration	No Separation problems
Additional equipment required	Yes	Little	No
Catalyst recycling	Possible	Easy	Not necessary
Cost of catalyst loses	High	Minimal	Minimal

Table 3. Catalyst removal in homogeneous and heterogeneous catalysis.

The solid nature of the heterogeneous catalyst gives it certain advantages over its homogeneous counterpart. The main advantage being the ease with which it can be separated from the reaction products (Table 3). However, it is evident from Table 2 that heterogeneous catalysts also have some major disadvantages, namely the variable activity and selectivity. This results from the tendency of solid-state catalysts to have a multitude of different reaction sites, each with differing properties. It is possible that only one of these is active for a particular reaction; the others may be inactive or catalyse undesirable reactions. Steric and/or electronic modification of the active sites is extremely difficult, if not impossible.

Conversely, homogeneous transition metal catalysts usually contain only one type of active site for each metal centre. Hence, in terms of activity per metal centre, homogeneous catalysts are frequently more active. Also, variation of the ligands around the metal may serve to improve the activity and selectivity of the catalyst. Whilst these attributes form a basis to utilise homogeneous catalysts, they remain under-used owing to difficulties with catalyst and product separation. The processes required to achieve separation normally lead to thermal stresses, which can cause catalyst decomposition and deactivation. Furthermore, the recovery processes are seldom quantitative giving rise to loss of productivity.

1.3.3 Biphasic Catalysis

In a two-phase system, the organometallic catalyst complex is molecularly well defined as with conventional homogeneous catalysts, but contains polar ligands which make it soluble in water or in another suitably polar solvent, and insoluble in less polar organic solvents.

In a biphasic reaction (Figure 13), the aqueous (or polar) phase containing the catalyst is mixed with the organic phase that contains the reactants. Reaction is catalysed in the aqueous phase or at the phase boundary; the catalyst is then removed from the products at the end of the reaction by simple phase separation.[2b] Therefore, thermal separation processes, which may cause catalyst degradation, are avoided. This major advantage is in addition to a number of other possible benefits. For example, the use of water as a polar phase is appealing since it is environmentally benign.

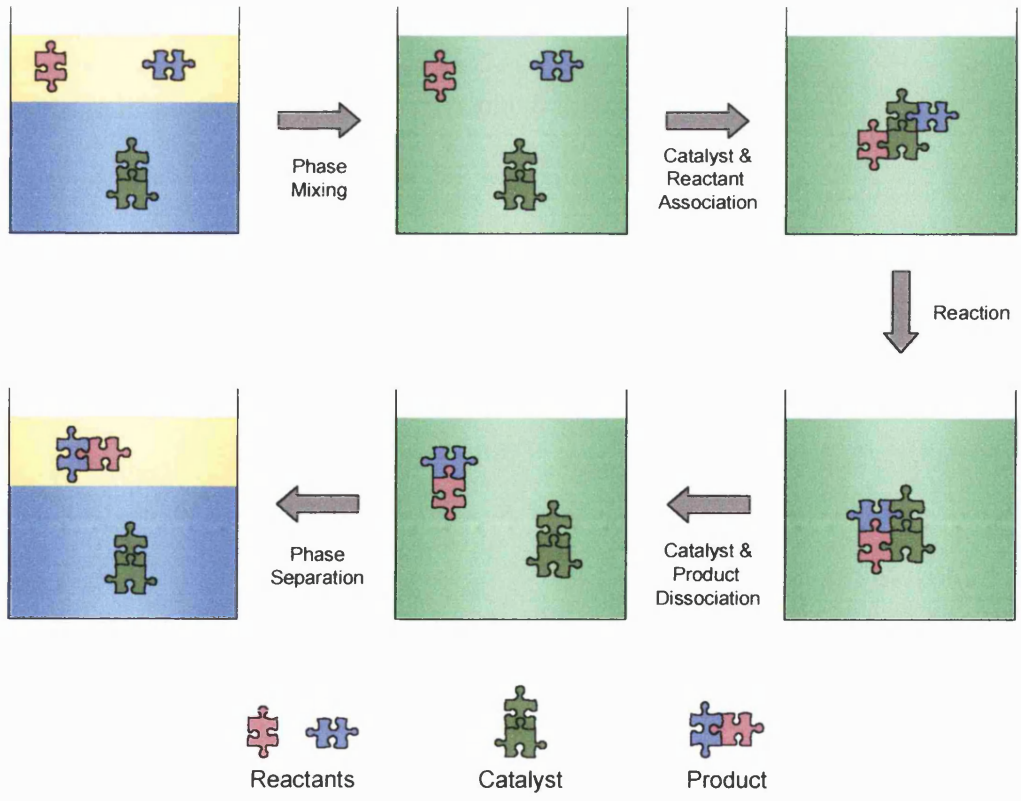


Figure 13. General principle of two-phase catalysis in water.

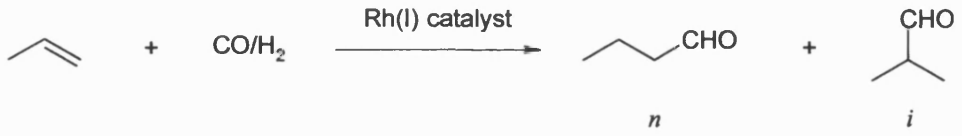
Although biphasic processes have proved effective in many cases, these reactions may be impeded by the substrate solubility in the aqueous layer in which the catalyst resides, and by a limited interfacial area. Also, reactions that take place at an interface may be unlike those that occur in the bulk because of the differing accessibility and orientation of the reactant molecules. For these reasons, the rate, selectivity and equilibrium position of given reaction may be altered.[86a]

1.3.3.1 Applications of Biphasic Catalysis

General interest in biphasic catalysis was sparked by the introduction of the Ruhrchemie/Rhône Poulenc biphasic hydroformylation process during the early 1980's.[2,72] Since then, intense research has led to the development of many biphasic reactions, some of which have been commercialised. The following discussion is limited to a few examples of well-established reactions in order to demonstrate the importance and application of aqueous two-phase catalysis.[73]

Hydroformylation

The Ruhrchemie/Rhône Poulenc process for the hydroformylation of propene is, without doubt, the most significant biphasic industrial procedure. Production of butyraldehyde is currently greater than 300,000 tonnes per annum. Originally, the rhodium(I) complex $HRh(CO)(TPPTS\text{-}Na)_3$ was the catalyst at the centre of this process. However, continual improvements in terms of catalyst activity and selectivity were made throughout the 1990's. This was achieved through the substitution of TPPTS-Na for the newly developed sulfonated phosphines, NORBOS-Na and BINAS-Na (Scheme 30).[6,7] From economic and environmental aspects, the two-phase process for hydroformylation has proved to be more viable than the original cobalt-based process and other modern Rh-based procedures.[74] Extension of this methodology to the hydroformylation of higher alkenes is currently an active area of research.[75]

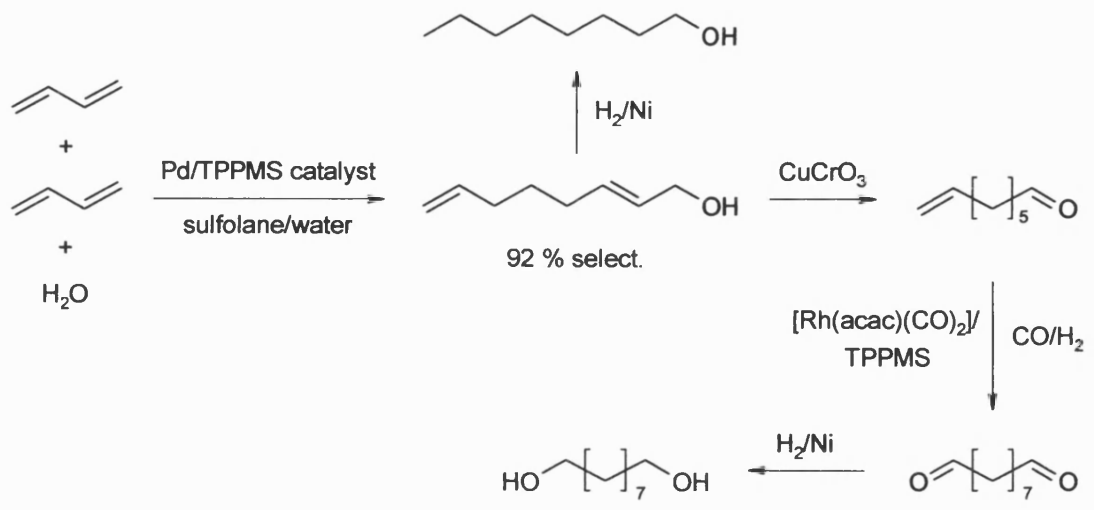


Catalyst System	Activity	Normal (*n*)	Branched (*i*)
Rh(I)/TPPTS-Na	1	94	6
Rh(I)/NORBOS-Na	118	81	19
Rh(I)/BINAS-Na	178	98	2

Scheme 30. Production of butyraldehyde from propene.

Hydrodimerisation

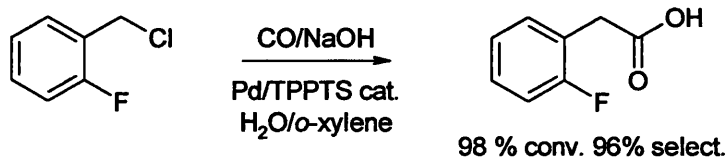
Another bulk process which utilises aqueous two-phase catalysis is the hydrodimerisation of 1,3-butadiene and water.[76] This is carried out by Kuraray in Japan for the manufacture of 1,9-nonanediol and 1-octanol (Scheme 31). The initial hydrodimerisation step utilises a palladium catalyst modified with the lithium salt of TPPMS, in the formation of 2,7-octadien-1-ol. Simple hydrogenation of 2,7-octadien-1-ol yields 1-octanol, a valuable plasticiser alcohol. Alternatively, isomerisation of 2,7-octadien-1-ol followed by biphasic hydroformylation results in a ω,ω'-dialdehyde, which is then hydrogenated to 1,9-nonanediol.



Scheme 31. The Kuraray process for the production of 1-octanol and 1,9-nonanediol.

Carbonylation

Palladium-catalysed carbonylation of substituted benzyl chlorides represents an effective route to phenylacetic acids (Scheme 32), which are valuable intermediates in the manufacturing of pharmaceuticals, cosmetics and fragrances.[77] Kohlpaintner and Beller have demonstrated the application of this reaction under biphasic conditions, thus increasing the industrial viability of this route to phenylacetic acids. The currently used procedure for industrial manufacture starts with the corresponding benzyl chloride, which is converted by a chloride/cyanide exchange to the benzyl cyanide. Subsequent hydrolysis with sulfuric acid yields the desired phenylacetic acids. During this two-step process, large amounts of salt (sodium chloride and ammonium sulfate) are produced, which is a considerable drawback. The new biphasic procedure creates 60 % less salt. Also, the introduction of a carbon atom using a cyanide molecule is fairly expensive in comparison with using carbon monoxide.

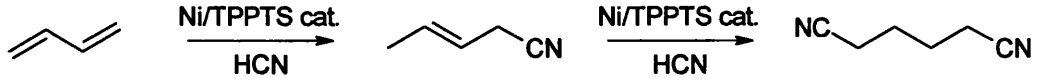


Scheme 32. Carbonylation of benzyl chlorides as a route to phenylacetic acids (R = H, Cl, F).

Hydrocyanation

Hydrocyanation reactions are potentially useful in generating new nitrogenous products, which are useful intermediates. These reactions include the addition of hydrogen cyanide to C=C, C=O and C=N double bonds to create alkyl nitriles, cyanohydrins and aminonitriles, respectively. Biphasic hydrocyanation catalysis is an emerging area of technology. Rhône Poulenc has investigated this field for the preparation of adiponitrile from hydrogen cyanide and butadiene (Scheme 33). Whilst the toxicity, expense and handling difficulties are drawbacks of using hydrogen cyanide as an organic building

block, the versatility of the nitrile functional group is a significant advantage. Also, the full miscibility of hydrogen cyanide with water makes it an ideal reagent for use in aqueous catalysis.[78]

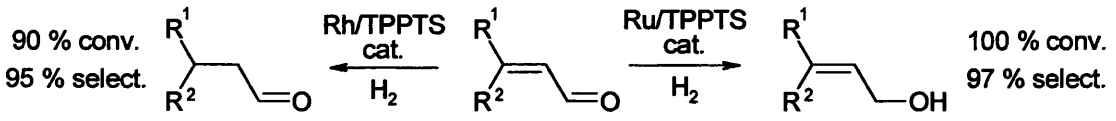


Scheme 33. Production of adiponitrile using biphasic catalysis.

Hydrogenation

The reduction of achiral unsaturated substrates was one of the first applications of aqueous biphasic catalysis,[79] and there are now many communications concerning a variety of catalysts and substrates. Enantioselective hydrogenation of prochiral substrates has also been thoroughly investigated.[80] Unfortunately, most biphasic systems performed poorly in comparison with their homogeneous counterparts. This was attributed to the poor solubility of molecular hydrogen and/or unsaturated substrate in the aqueous phase, in which the catalyst was contained. Addition of co-solvents such as methanol or ethanol to the two-phase hydrogenation systems often produced an improvement in reaction rate and selectivity.

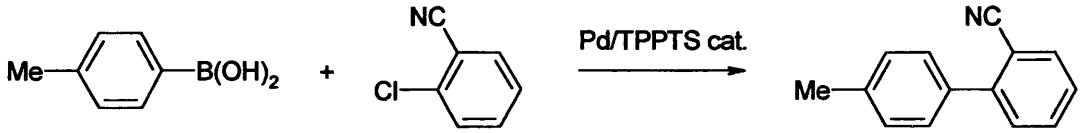
One valuable application in which biphasic hydrogenation excels is the selective reduction of α,β-unsaturated aldehydes. Ruthenium(II) complexes of TPPTS catalyse the reduction of various α,β-unsaturated aldehydes to the corresponding unsaturated alcohols under relatively mild conditions and short reaction times. On the other hand, rhodium(I) complexes of TPPTS preferentially promote the reduction of C=C double bonds, thus forming the corresponding saturated aldehyde (Scheme 34).[81]



Scheme 34. Biphasic hydrogenation of α,β-unsaturated aldehydes ($R^1 = R^2 = Me$).

Suzuki Coupling

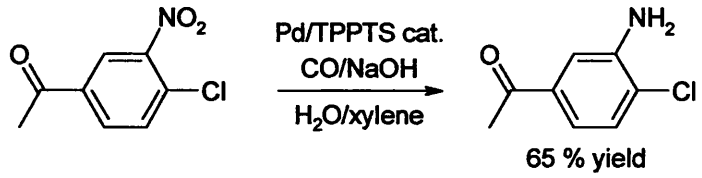
The palladium-catalysed Suzuki coupling of aryl halides with arylboronic acids under aqueous conditions has been achieved by Genêt.[82] Although this methodology proved effective, it was considered unsuitable for scale-up owing to the use of expensive iodinated and brominated aromatics. However, less expensive chlorinated derivatives are currently utilised in an aqueous procedure, which is operated on a commercial scale by Clariant (Scheme 35).



Scheme 35. Biphasic Suzuki coupling.

Selective Reduction of Aromatic Nitro-Compounds

Tafesh and Beller developed a unique two-phase system for the reductive carbonylation of substituted nitroaromatics to the corresponding aniline (Scheme 36).[83] This technique enables the reduction of the nitro- group in the presence of other sensitive functionalities.



Scheme 36. Aromatic amines via the reductive carbonylation.

Besides those discussed above, there are additional catalytic reactions which have been adapted to operate under biphasic conditions. These include Heck coupling[35c,84] and ring opening metathesis polymerization (ROMP).[73] Also, alternative non-aqueous biphasic systems exist (e.g. immiscible organic phase systems, fluorous biphasic systems[85]), which may be of commercial interest in future years.

1.3.4 Supported Aqueous Phase Catalysis

In principle, immobilisation using a solid support may be achieved in several ways: physical or chemical adsorption of the metal complex onto the support; entrapment of the metal complex via *in situ* synthesis within zeolites; and dissolution of the metal complex in a non-volatile solvent that is adsorbed onto the surface of a support (SAPC). The first two methods of immobilisation have led to active 'heterogenised' catalysts. However, it was found that the immobilised systems never approached the combined activity/selectivity performance levels of their homogeneous counterparts. Also, significant leaching of the catalyst or associated compounds meant that these systems had a limited lifespan.[86a]

It is evident that there are two conditions that must be fulfilled in order to create an effective solid supported catalyst. Firstly, immobilisation of the catalyst complex must be sufficient to ensure minimal leaching; and secondly, the catalyst must have adequate mobility whilst *upon the support.* This ensures that it may undergo the changes in spatial configuration which are typical of the catalytic cycle in a homogenous process. It is usually difficult to satisfy these two conflicting requirements, since the process of immobilsation will not only prevent the catalyst moving away from the support and into the bulk solution, but will also hamper its mobility upon the surface of the support. Indeed, it seems that this is the case in the first two approaches to immobilisation described above, and is a possible reason for the relatively poor activity/selectivity observed in such systems. However, the technique of supported aqueous phase catalysis should provide a system in which the catalyst is 'heterogenised' whilst having the required mobility upon the solid support.

SAP catalysts consist of a water-soluble organometallic complex dissolved in a thin film of water (or another suitably polar solvent) that is supported on a high-surface-area hydrophilic solid such as controlled pore glass (CPG). During reaction (Figure 14),

reactant molecules diffuse from the bulk organic liquid phase into the porous catalyst. Reaction is catalysed at the water-organic interface and the products diffuse back into the organic phase. Immobilisation of the catalyst is brought about because of the insolubility of the hydrophilic complex in the bulk organic media. However, the complex is completely mobile within the polar solvent upon the support. The high surface area of controlled pore glass (1g of CPG-240 has a surface area of 77.5 m^2) provides the necessary interfacial area for reaction to occur at a reasonable rate; an attribute which biphasic catalysis often lacks. Also, in contrast to many other supports, CPG is stable to mechanical and thermal fatigue.

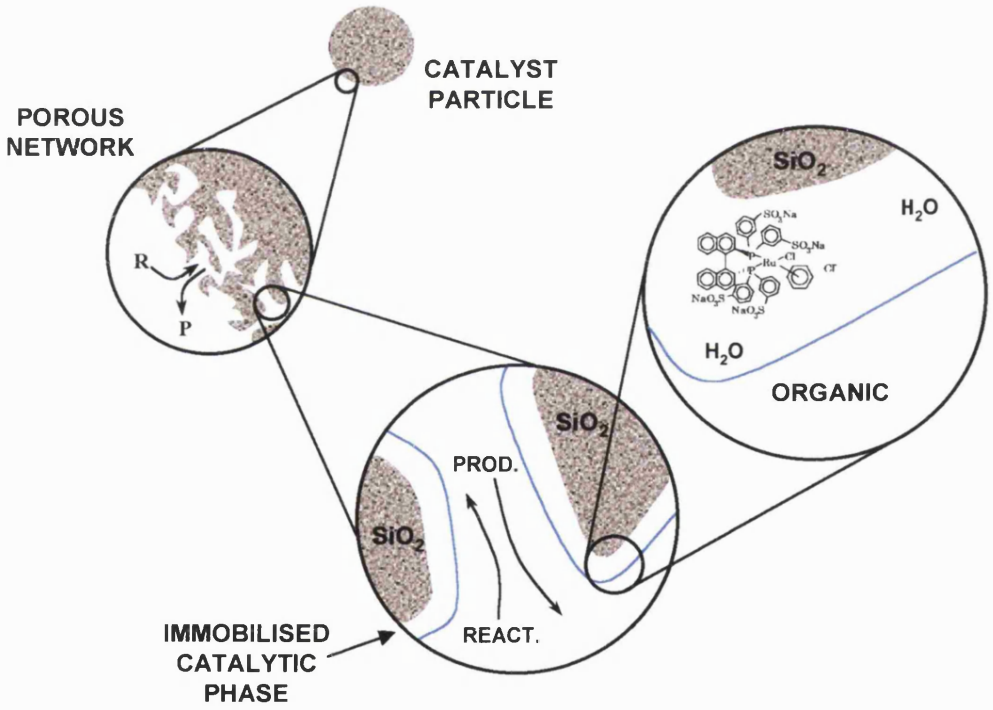


Figure 14. A schematic diagram of a SAP catalyst used in asymmetric hydrogenation.

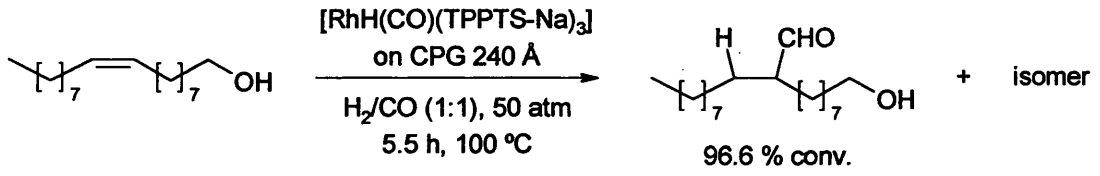
1.3.4.1 Applications of Supported Aqueous Phase Catalysis

Supported aqueous phase catalysis has been applied to various transition-metal catalysed reactions. An in depth review of this area was communicated in 1998.[87] Since then, the few papers regarding this subject have concentrated on hydroformylation reactions.[88]

The following discussion briefly describes some of the results obtained using SAPC in the fields of rhodium-catalysed hydroformylation, ruthenium-catalysed asymmetric hydrogenation and palladium-catalysed Heck coupling reactions.

Hydroformylation

The technique of SAP catalysis was first demonstrated by Davis and co-workers in 1989.[86b] A SAP rhodium hydroformylation catalyst was prepared by combining an aqueous solution of $[RhH(CO)(TPPTS\text{-}Na)_3]$ with CPG 240 Å and additional TPPTS-Na. Removal of the solvent (water) by evaporation provided a 'dry' catalyst with a water content of 2.9 %.[86c] The SAP catalyst was then used to hydroformylate liquid-phase olefins, which are usually water insoluble and therefore not hydroformylated under standard biphasic conditions. For example, oleyl alcohol was converted into the corresponding aldehyde products in 96.6 % yield (Scheme 37). Surprisingly, analysis of the organic phase revealed that no leaching of the rhodium catalyst had occurred during reaction.[86a] It has been demonstrated that the individual components of the supported catalyst can self assemble under the reaction conditions required for hydroformylation. This implies that the reverse process, which results in leaching, is unlikely.[86c]



Scheme 37. Hydroformylation of oleyl alcohol using SAPC.

The water content of the $[RhH(CO)(TPPTS\text{-}Na)_3]$-based SAP catalyst has been shown to greatly influence the activity of the catalyst. Davis and co-workers reported maximum activity at a water content of approximately 8 wt%. At this level the catalyst has a high degree of mobility whilst still being available at the interface. A lower water content

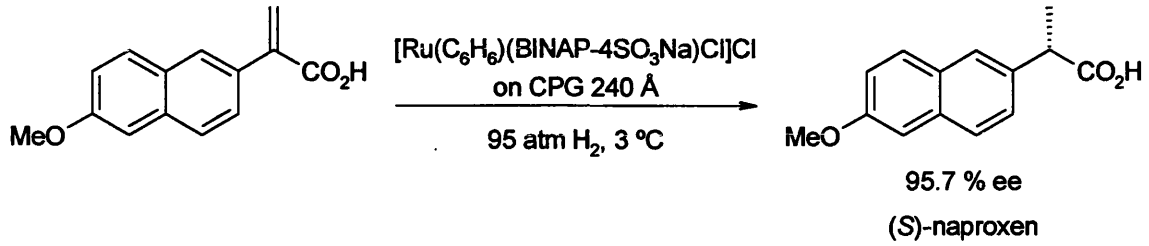
suppresses catalyst mobility as reflected by the reduced activity, and a higher water content renders the catalyst less available to the water insoluble substrates. The TOF for the hydroformylation of 1-heptene increases by two orders of magnitude when increasing the water content of the catalyst from 2.9 wt% to 9 wt%.[86e] Variation in the degree of hydration was achieved by exposing the catalyst to water vapour of a known pressure for different time periods. The regioselectivity of the reaction was also found to depend on the water content of the catalyst. For example, the normal:branched ratio of aldehyde products for the hydroformylation of 1-octene varied between 2.15 and 2.9. This has been attributed to a variation in catalytic pathway.[87]

Hovárth has also investigated the dependence of catalytic activity on water content. Starting with a high water content, the activity of the catalyst in a trickle bed reactor was seen to increase as water leached from the support into the organic layer, until the quantity of water was only sufficient to supply two monolayers to the surface of the CPG. Having such a low water content, Hovárth proposed that the hydrophilic support holds the water-soluble phosphines of the organometallic catalyst by hydrogen bonding of the hydrated sodium-sulfonate groups to the surface.[89] Indeed, a recent report has described the immobilisation of rhodium-phosphine complexes via hydrogen bond interactions between the silanol groups of the silica and sulfonate functionalities of the phosphine ligands.[90] Reports communicated recently, concerning SAP hydroformylation catalysts, further detail the influence of support hydration and surface characteristics upon catalyst activity and regioselectivity;[88c] and also comment on the proposal of Hovárth.[88b]

Asymmetric hydrogenation

Wan and Davis constructed a SAP hydrogenation catalyst which incorporated the polar ruthenium complex $[Ru(C_6H_6)(BINAP\text{-}4SO_3Na)Cl]Cl$. The substrate of choice was

2-(6-methoxy-2-naphthyl)acrylic acid, whose hydrogenation product is the high-value, non-steroidal anti-inflammatory drug, naproxen (Scheme 38).[8c] Studies using this substrate and catalyst complex were also undertaken in homogeneous and biphasic systems containing aqueous media.



Scheme 38. Asymmetric hydrogenation of 2-(6-methoxy-2-naphthyl)acrylic acid.

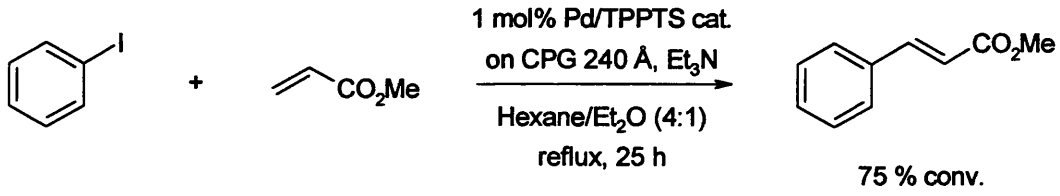
The 'dry' (1.9 wt% water) SAP catalyst proved to be inactive. However, hydration gave rise to a catalytic system whose activity was just seven times less than that of the corresponding homogeneous system, and fifty times greater than that observed in the biphasic (ethyl acetate/water) system. Once again, a relationship between catalyst activity and water content was observed. That is, increasing the loading of water produced an increase in activity. In this system, ethyl acetate was used as the bulk solvent, and the extent of hydration was controlled by the solubility of water in this solvent.

Unfortunately, the enantiomeric excess observed in the SAP system (and biphasic) was nearly 20 % less than that of the non-aqueous homogeneous system. Wan and Davis proposed that the chloro-ligand of the ruthenium complex is easily lost in the aqueous systems through hydrolysis, which causes a change in the configuration of the catalyst and a resultant deterioration in enantioselectivity. Substitution of water as the support solvent for ethylene glycol gave rise to a catalyst which was able to hydrogenate 2-(6-methoxy-2-naphthyl)acrylic acid with an enantioselectivity of 95.7 %. However, unlike the original hydrated SAP catalysts, traces of ruthenium were found in the bulk organic

phase. This is likely to be the result of ethylene glycol being three times more soluble than water in ethyl acetate. An alternative method of catalyst preparation was devised, which proved effective in combating the ruthenium leaching.

Heck Coupling

Research undertaken within the group has centred on the application of supported palladium catalysts in Heck coupling, Suzuki coupling and allylic substitution reactions.[91,87] The Heck reaction of iodobenzene with methyl acrylate to afford the coupled product methyl cinnamate was achieved using a palladium/TPPTS-Na catalyst, which was supported in a film of ethylene glycol upon CPG (Scheme 39). Using this metal-ligand combination, less than 1 ppm of palladium was leached into the bulk organic phase. Substitution of TPPTS-Na for TPPMS-Na gave rise to a catalyst which was retained less upon the support, as indicated by higher palladium leaching. This may be attributed to the greater hydrophilic nature of the Pd/TPPTS-Na complex. Recycling of the supported catalyst proved successful. However, the reaction yield diminished as the number of recycle runs increased. This is likely to be the result of phosphine oxidation, which renders the catalyst less effective.[92]



Scheme 39. Heck coupling using a supported palladium catalyst.

As a method of immobilisation, supported liquid phase catalysis has proved effective. Many transition metal catalysed reactions are yet to be examined using this technique. However, as the area of water-soluble organometallic catalysts expands, so can the field of SAPC.

Chapter 2

Results and Discussion

2.1 Aims and Objectives

The objective of this project was to design and synthesise polar catalysts for the efficient asymmetric transfer reduction of ketones. Ultimately, these catalysts would operate in supported aqueous phase and biphasic systems, thus providing a convenient route to enantiomerically enriched alcohols, which are free from transition metal residues.

2.1.1 Envisaged Programme of Work

Initial studies would concentrate on the synthesis of suitable polar catalysts. Hence, this involves the preparation of polar or charged ligands; these would have the same topology as successful non-polar ligands existing in the literature. Catalysts would initially be tested in homogeneous systems using simple aromatic ketones as substrates and conventional hydride sources. After optimisation studies, the most effective catalysts would be used in the development of biphasic and supported aqueous phase catalytic systems. The success of these techniques would then be established by the measurement of transition metal residues in the reaction product.

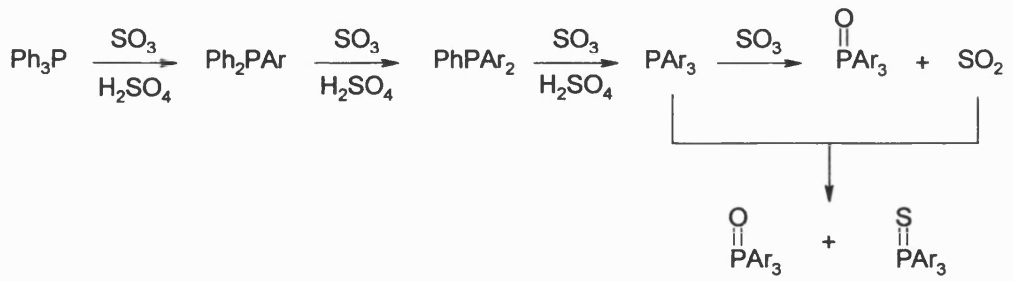
2.2 Synthesis of Polar Ligands

2.2.1 Sulfonated Phosphines

At the outset of the project several non-polar phosphine-based catalysts had been reported for the transfer hydrogenation of aromatic ketones.[93] Therefore, it was envisaged that a suitable water-soluble catalyst could be constructed using polar phosphine ligands. An abundance of achiral and chiral phosphines had appeared in the literature, which would allow for subtle changes in the catalyst design. Initial method development would use trisulfonated triphenylphosphine (TPPTS-Na) in the formation of an achiral catalyst. Bäckvall had already reported some success using the ruthenium(II) catalyst, $RuCl_2(PPh_3)_3$ for the transfer hydrogenation of acetophenone.[59]

2.2.1.1 Trisulfonated Triphenylphosphine (TPPTS-Na)

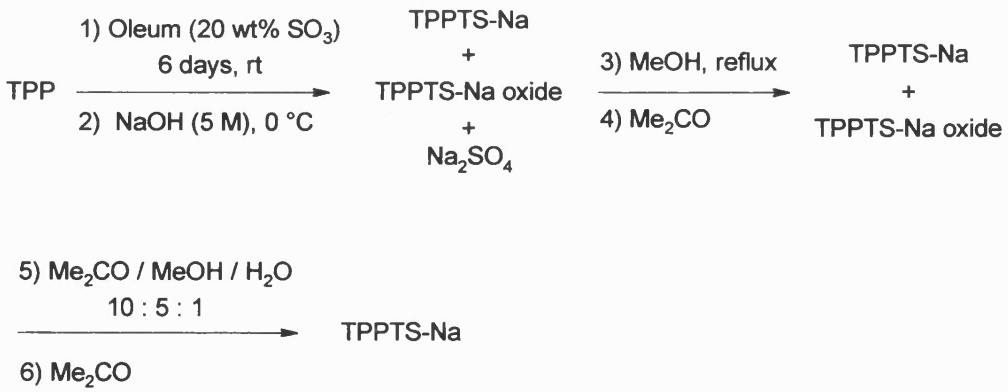
The preparation of TPPTS-Na **1** is not trivial; this is demonstrated by the number of communications for its synthesis.[4,5] Synthetic procedures are often cumbersome and difficult to reproduce because of phosphine oxide formation during the reaction. In 1974, Rhône-Poulenc reported a method for the synthesis of TPPTS-Na, based on the electrophilic aromatic substitution of triphenylphosphine (TPP) using oleum (i.e. concentrated sulfuric acid containing 20 % by weight of SO_3) at 40 °C during one day.



Scheme 40. Typical reactions in the sulfonation of triphenylphosphine (Ar = *m*-$C_6H_4SO_3H$)

After hydrolysis and neutralisation by sodium hydroxide, an aqueous solution of sodium sulfate and a mixture of different phosphorus compounds (Scheme 40), consisting mainly of TPPTS-Na and the corresponding phosphorus oxide (TPPTS-Na oxide), were obtained. Purification was achieved by exploiting the differing solubilities of these compounds in methanol/water mixtures.[94]

A procedure based on this original synthesis was attempted[5b] (Scheme 41). After work-up, the crude product contained a 3:2 mixture of TPPTS-Na and TPPTS-Na oxide as determined by ^{31}P NMR (δ = 35.1 (P=O) and -5.4 (P)). Bartik and co-workers developed a solvent system in which the solubilities of TPPTS-Na and its oxide were different. Addition of acetone to a solution of the crude material in this solvent mixture allowed the selective precipitation of TPPTS-Na. Several attempts at purification using this procedure failed, with no significant change in the phosphine oxide content. With this purity, the TPPTS-Na was not suitable as a component for catalyst synthesis.



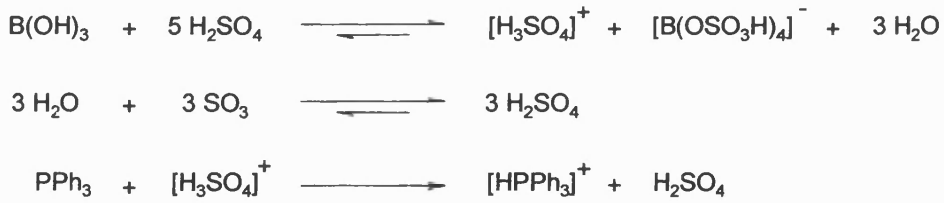
Scheme 41. Synthesis and purification of TPPTS-Na according to Bartik.

Subsequent communications regarding the synthesis of TPPTS-Na have suggested that the extent of phosphine oxide formation is influenced by the pH during the work-up stages[5d] and also by mode and speed of agitation.[5a]

2.2.1.2 Disulfonated Triphenylphosphine (TPPDS-Na)

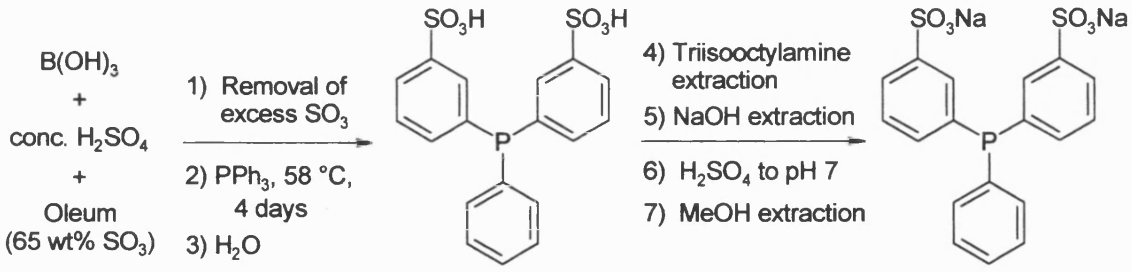
Herrmann and co-workers had reported a technique for the sulfonation of triphenylphosphine using $SO_3/H_2SO_4/H_3BO_3$, a superacidic medium in which the formation of phosphine oxides was reduced considerably.[5c] However, they found that the selectivity towards TPPTS-Na in this method was very poor, with the disulfonated derivative of triphenylphosphine (TPPDS-Na) being the predominant product. Nevertheless, TPPDS-Na would be a suitable ligand for the construction of a polar catalyst; hence, its synthesis was attempted.

Dissolution of *ortho*-boric acid in concentrated sulfuric acid forms $[H_3SO_4]^+$, which is assumed to be the active electrophilic species in the sulfonation mixture (Scheme 42). The water that forms in this process is then quantitatively 'titrated' by oleum to generate a superacidic medium, which should have significantly less oxidising power than oleum itself. On addition of the phosphine to this mixture, protonation occurs, which also provides stability against oxidation.



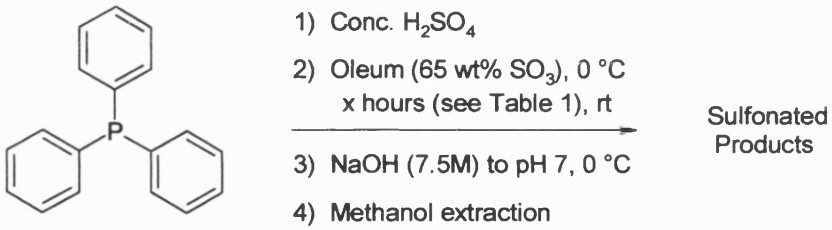
Scheme 42. Formation of a non-oxidising medium for the sulfonation of arylphosphines.

Scheme 43 summarises the entire procedure, which was attempted several times but without success. ^{31}P NMR revealed that the reaction product contained not only a phosphine (δ = -6.0), but also a minimum of 30 % phosphine oxide (δ = 34.3). This suggests that the method for removing the excess sulfur trioxide (high vacuum, 60 °C, 1 hour) was not effective. Also, very poor yields (5 – 12 %) indicate that the extraction procedure was unsuccessful, maybe as a result of over-sulfonation.



Scheme 43. Synthesis of TPPDS-Na by Herrmann.

A closer look at the sulfonation process using oleum led to the design of a quick and reliable synthesis of TPPDS-Na. It was known that protonation of the phosphine helps protect against the oxidising effects of oleum, and also that oxidation was more likely to occur at elevated temperatures. With these facts in mind, a simple method was designed to follow the extent of sulfonation of triphenylphosphine (Scheme 44).



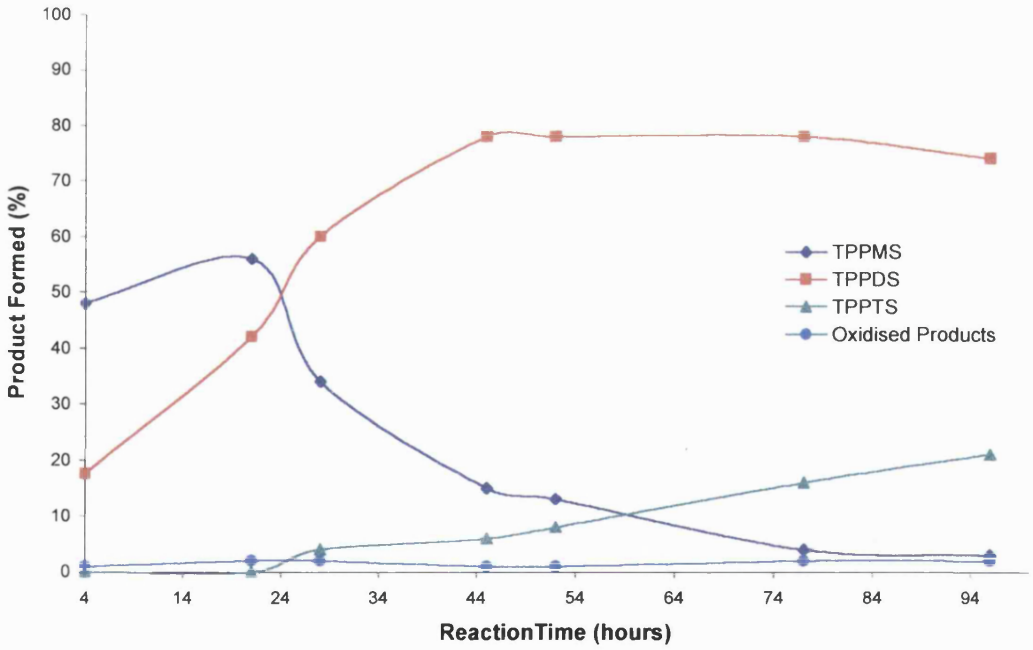
Scheme 44. Procedure for following the extent of sulfonation.

Initial dissolution of the triphenylphosphine in concentrated sulfuric acid minimises the chance of oxidation on addition of oleum. Also, neutralisation of the reaction mixture is an extremely exothermic process and therefore must be carried out very slowly at 0 °C; this further reduces the chance of phosphine oxide formation. Following the addition of oleum the reaction was allowed to proceed at room temperature. After the allowed reaction time an aliquot was removed, subjected to a work-up procedure and then ^{31}P NMR used to determine the relative percentage of the various sulfonated products (Table 4 & Graph 2). Triphenylphosphine is consumed within a matter of hours, rapidly forming the monosulfonated derivative (TPPMS). Further sulfonation yields TPPDS

and TPPTS, although the formation of TPPTS is relatively slow. At any one time-point between 4 and 96 hours the mixture contains two or more sulfonated products. It can also be seen that the percentage of oxidised material remains insignificant.

Time (hours)	TPP (%)	TPPMS (%)	TPPDS (%)	TPPTS (%)	Oxidised Products (%)
4	3.5	48	17.5	0	1
21	0	56	42	0	2
28	0	34	60	4	2
45	0	15	78	6	1
52	0	13	78	8	1
77	0	4	78	16	2
96	0	3	74	21	2

Table 4. Sulfonation products of triphenylphosphine



Graph 2. Sulfonation of triphenylphosphine: Concentration – time profile.

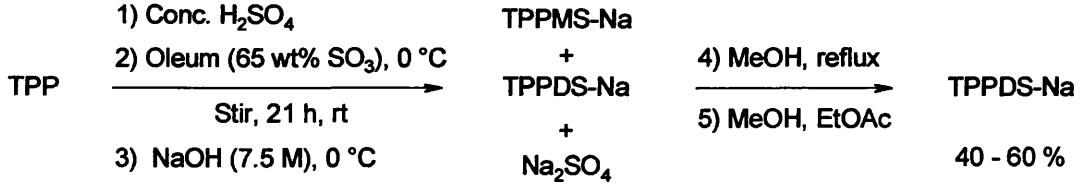
Additional individual sulfonation experiments were conducted for longer time periods; the results of which are summarised in Table 5. It can be seen that further sulfonation of

TPPDS to TPPTS occurs relatively slowly. Also, the percentage of oxidised products becomes significant after 6 days. Sulfonation experiments were also carried out at 40 °C for comparison. At this temperature the rate of sulfonation and phosphine oxidation is increased.

Time (days)	TPPMS (%)	TPPDS (%)	TPPTS (%)	Oxidised Products (%)
4	0	75	22	3
6	0	63	33	4
12	0	48	40	12

Table 5. Sulfonation products of triphenylphosphine (4 – 12 days)

With the results from these experiments it was possible to develop a synthesis for TPPDS-Na (Scheme 45). It was chosen to stop the sulfonation reaction at about 21 hours, because at this time only TPPMS and TPPDS were present in the reaction mixture; separation of these would be straightforward. Thus, after neutralisation, a mixture containing sodium sulfate, TPPMS-Na and TPPDS-Na was obtained. Extraction with methanol removed the sulfonated phosphines from the sodium sulfate. Separation of TPPDS-Na and TPPMS-Na was achieved by dissolving the crude mixture in methanol and then precipitating TPPDS-Na by adding ethyl acetate.

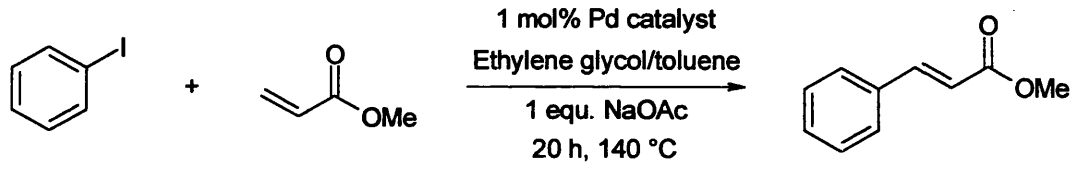


Scheme 45. Synthesis of TPPDS-Na

This method allows the synthesis of pure TPPDS-Na with a modest yield. Higher yields may be obtained by allowing the reaction to proceed for longer but the product will have a lower purity due to contamination with TPPTS-Na.

The utility of TPPDS-Na as a polar ligand was demonstrated in a biphasic palladium-catalysed Heck coupling[84a] reaction. For comparison, TPPTS-Na and TPPMS-Na were also subjected to the same experimental procedure.

A palladium catalyst was prepared *in situ* via the reaction of palladium dichloride and the desired sulfonated phosphine ligand in ethylene glycol. The catalytic solution was then vigorously stirred at 140 °C with a non-polar phase consisting of methyl acrylate **52**, iodobenzene **51**, sodium acetate and toluene (Scheme 46). After a 20-hour reaction time, the toluene phase was isolated and analysed; the results are given in Table 6.



51 **52** **53**

Scheme 46. Biphasic Heck coupling reactions.

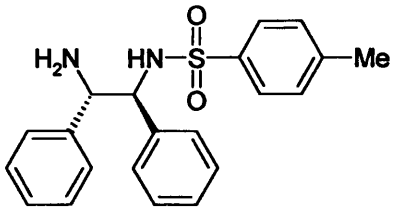
Ligand	Isolated Yield of **53** (%)	Pd Leaching (ppm, %)
TPPMS-Na	85	3.5, 0.3
TPPDS-Na	88	1.8, 0.2
TPPTS-Na	87	2.3,0.2

Table 6. Results of the Pd-catalysed biphasic Heck coupling of methyl acrylate and iodobenzene.

It is evident that each catalyst is effective in the formation of methyl cinnamate **53**. More importantly, leaching levels are also comparable; the percentage leaching represents the amount of palladium contamination with respect to the quantity of palladium catalyst employed.

2.2.2 Enantiomerically Pure Ligands

Perhaps the most significant development in the area of transfer hydrogenation has been the introduction of mono-tosylated diamine ligands (Section 1.2.2). In particular, ligands **37** (TsDPEN) and **38** (TsCYDN) have been complexed with ruthenium(II), rhodium(III) and iridium(III) to form highly enantioselective catalysts.[62] Therefore water-soluble analogues of these ligands were thought to be attractive target molecules.



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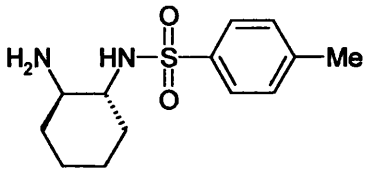
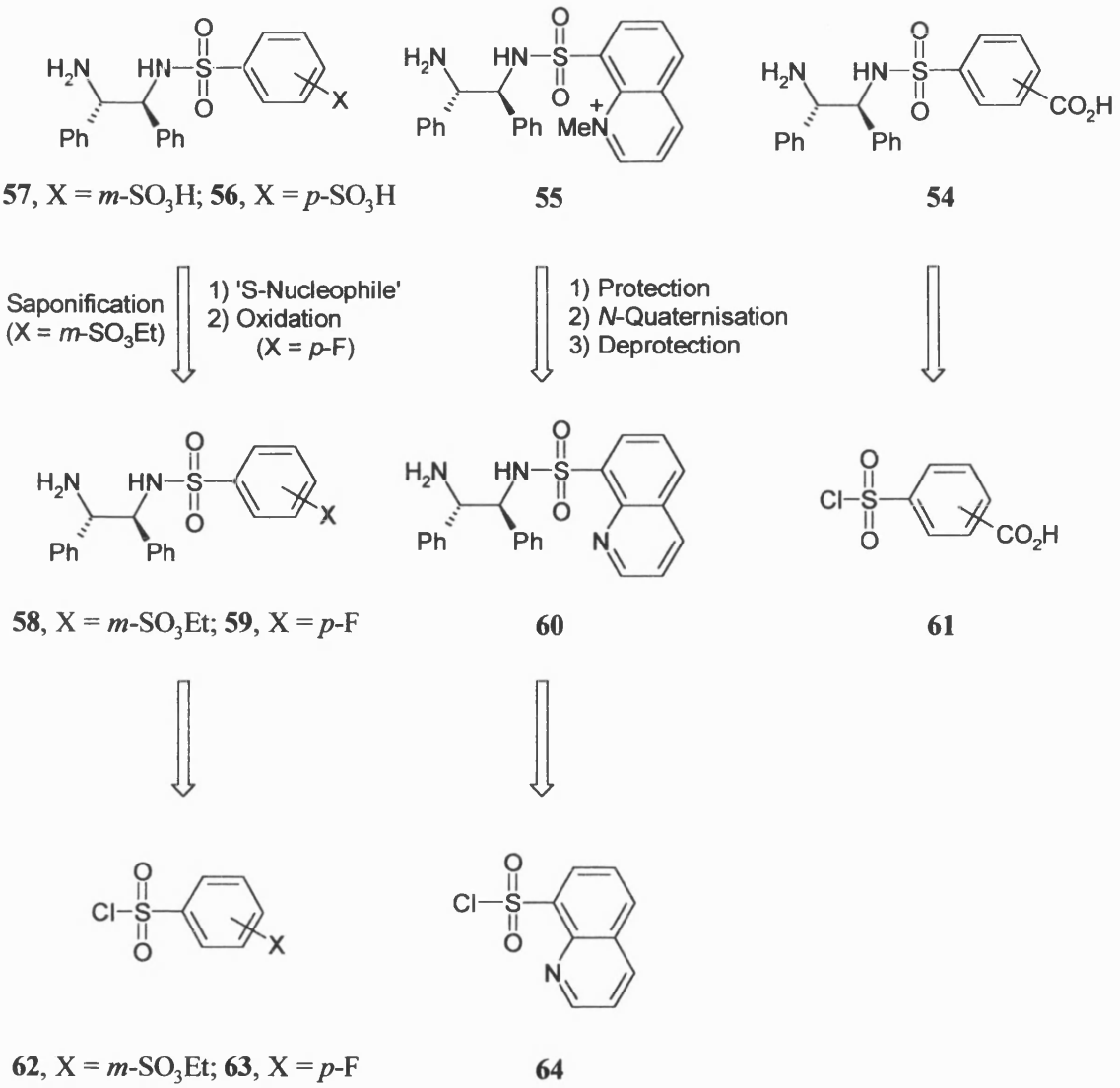


38

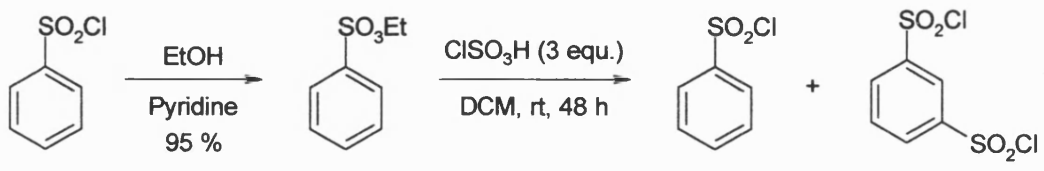
2.2.2.1 Background

Previous work in the group[95] examined the coupling of diphenylethylenediamine (DPEN) with functionalised arylsulfonyl chlorides (retrosynthetic analysis in Scheme 47) as a route to water-soluble analogues of ligand **37**. Accordingly, the synthesis of target molecule **54** containing a *meta*- or *para*-substituted carboxylic acid group was successful. Polywka and co-workers[69] had also used this approach to prepare *para*-substituted **54**. The synthesis of cationic target molecule **55** was not completed. Coupling of quinoline-8-sulfonyl chloride **64** with DPEN in the presence of triethylamine gave mono-sulfonamide **60** in high yield. Boc-protection of the primary amine was achieved, however quaternisation of the aromatic ring nitrogen was not attempted. Efforts to prepare target **58** incorporating a *meta*-sulfonic acid ethyl ester functionality failed due to difficulties in preparing precursor **62**. Reaction of excess chlorosulfonic acid with the ethyl ester of benzenesulfonic acid resulted in the formation of a mixture benzenesulfonyl chloride and benzene-1,3-disulfonyl dichloride (Scheme 48).

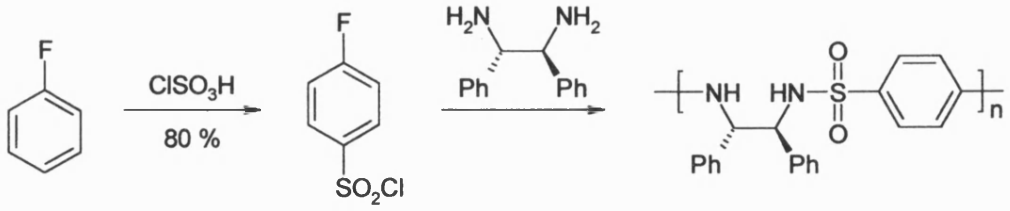


Scheme 47. Retrosynthetic analysis 1.

Attempts to prepare ligand **59** containing a *para*-fluoro group were also unsuccessful. It appeared that the coupling of 4-fluoro-benzenesulfonyl chloride with DPEN resulted in polymer formation, probably via nucleophilic substitution of the fluoro group with a free primary amine (Scheme 49).



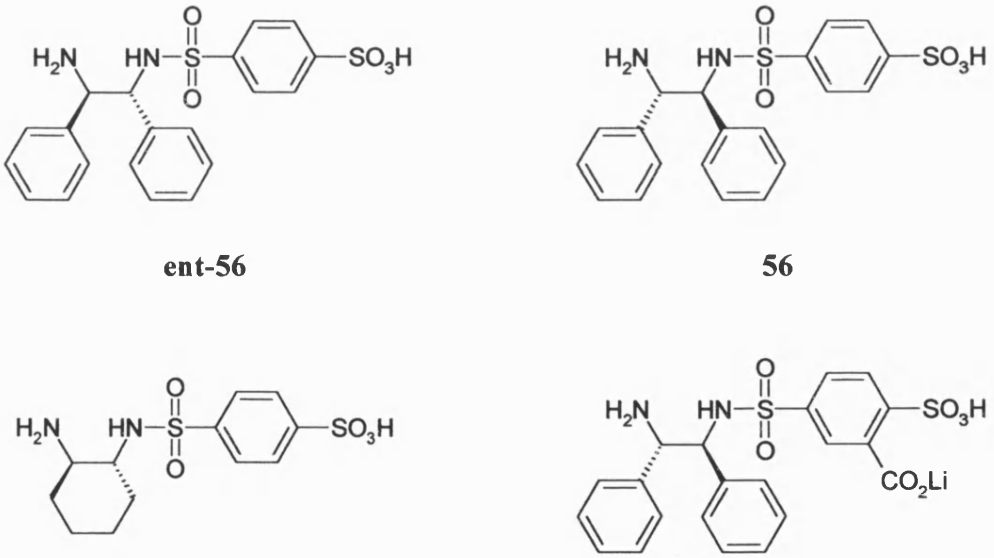
Scheme 48. Attempted synthesis of compound **62**.



Scheme 49. Attempted synthesis of sulfonamide **59**.

2.2.2.2 Synthesis of Polar Aminosulfonamide Ligands

During this project, polar analogues of Noyori's and Knochel's[62d] mono-tosylated diamine ligands have been prepared (Figure 15). The synthesis of each ligand relies upon the oxidation of a disulfide bond to create a sulfonic acid functionality.



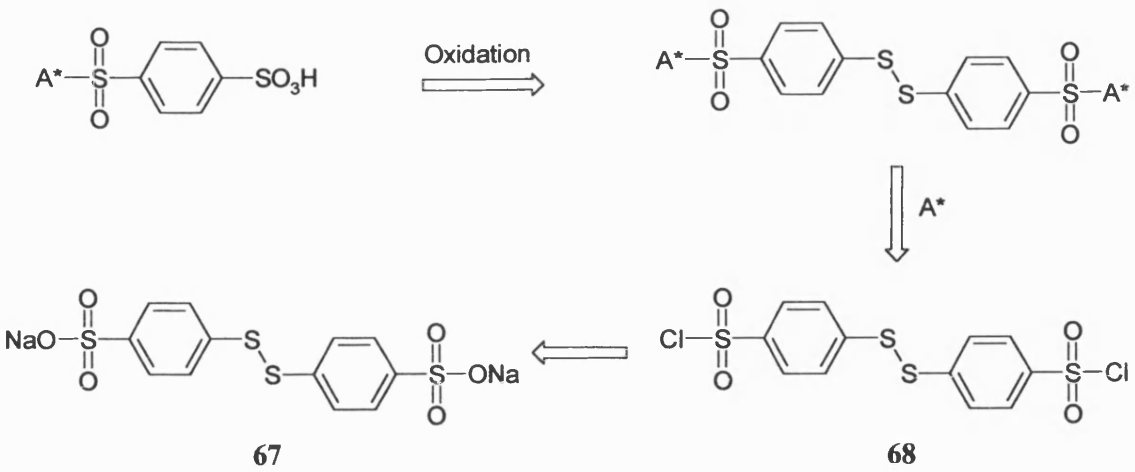
ent-56 **56**

65 **66**

Figure 15. Polar aminosulfonamide ligands.

Synthesis of Ligands 56, ent-56 and 65

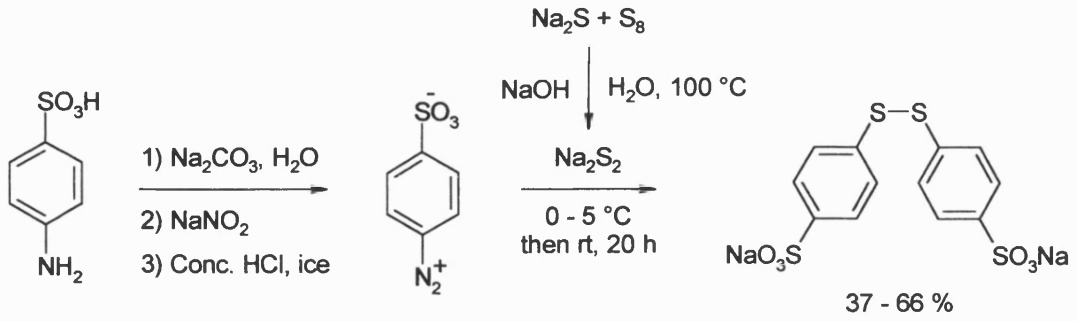
Retrosynthetic analysis (Scheme 50) shows that aminosulfonamide ligands of the form A*SO_2-*p*-$C_6H_4SO_3H$ where A* is a chiral diamine would be accessible from disodium 4-[(4-sulfonatophenyl)disulfanyl]benzenesulfonate **67**. Smith and co-workers had described a route to disulfide **67** starting from readily available sulfanilic acid.[96]



Scheme 50. Retrosynthetic analysis 2 (A* = chiral diamine).

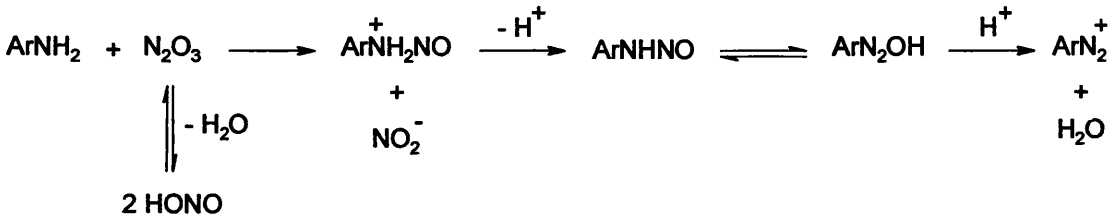
Synthesis of Disulfide 67

Disodium 4-[(4-sulfonatophenyl)disulfanyl]benzenesulfonate **67** was prepared from sulfanilic acid by reversed diazotisation followed by coupling with disodium disulfide (Scheme 51). Sulfanilic acid is sparingly soluble in water and is therefore solubilised with anhydrous sodium carbonate before the addition of sodium nitrite. The diazonium compound is formed as an internal salt or 'zwitterion'; this precipitates from the aqueous solution, forming a light brown suspension. Compounds of this type can be dangerously explosive when dry; therefore, isolation and storage must not be attempted. When stored at 15 °C (or below) the diazonium suspension is sufficiently stable and may be kept for several hours.



Scheme 51. Synthesis of disulfide **67**.

The mechanistic details of diazotisation are shown in Scheme 52. The actual nitrosating species varies according to reaction conditions and may be N_2O_3, NO^+, NOCl or $H_2NO_2^+$. In dilute acid N_2O_3 is the actual attacking species.[97]

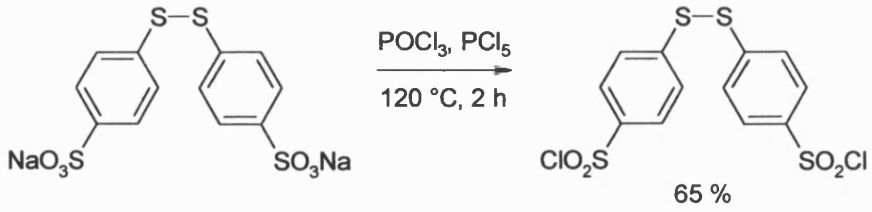


Scheme 52. Mechanism of diazotisation.

Disodium disulfide was produced by the reaction of sodium sulfide, elemental sulfur and sodium hydroxide in aqueous solution. Compound **67** results from the nucleophilic substitution of the diazonio group (N_2^+) with the disulfide (S_2^{2-}) anion. Yields for this procedure were variable (37 – 66 %), however, it was found that a 2-hour reaction time as stated in the literature procedure was insufficient; nitrogen evolution continued for more than 8 hours. Therefore, yields were maximised by allowing a 20-hour reaction time. The synthesis described was achieved without difficulties on a 200 g scale. Transfer of the diazonium suspension was then best accomplished using a fine teflon capillary and the action of gravity (siphon). However, whilst the large-scale synthesis is feasible it should be noted that hydrogen sulfide is also produced during the reaction; thus adequate fume extraction is vital.

The literature protocol characterised disulfide **67** only by microanalysis; hence additional analysis was obtained in order to confirm the structure. The ^{1}H NMR consists of a pair of doublets (AA'BB' system) demonstrating the *para*-substitution of the benzene rings. The electrospray mass spectrum (ES^-) exhibits an ion with *m/z* 399 (100 %) corresponding to $[M\text{-}Na^+]^-$.

Conversion to Sulfonyl Chloride 68



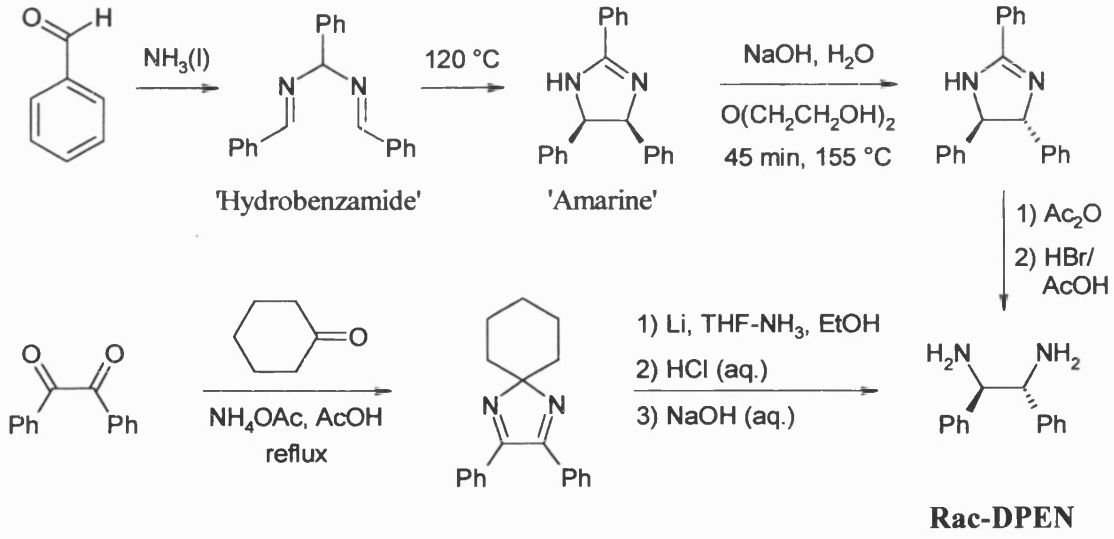
Scheme 53. Synthesis of sulfonyl chloride **68**.

Conversion of benzenesulfonic acid salt **67** to the corresponding sulfonyl chloride **68** was achieved using a mixture of phosphorus pentachloride and phosphorus oxychloride at reflux (Scheme 53). On completion of the reaction, excess $PCl_5/POCl_3$ was hydrolysed by adding the reaction mixture (first diluted with dichloromethane) to ice. A series of extractions then allowed the separation of compound **68** from inorganic acids and salts. The modest yield of the reaction is probably the result of hydrolysis of the sulfonyl chloride functionality. It was expected that under the conditions of the work-up (acidic and basic), hydrolysis would be a significant problem. However, it seems that conversion of the sulfonyl chloride to the corresponding acid occurs relatively slowly. On a larger scale (50 g), the work-up procedure was more time consuming, which resulted in a greater extent of hydrolysis and therefore produced a lower reaction yield (37 – 45 %). The characterisation data available from the literature for sulfonyl chloride **68** consist of a melting point and microanalysis.[98] Thus, ^{1}H and ^{13}C NMR, infrared, and accurate mass spectra were obtained in addition to a melting point and microanalysis.

Synthesis and Resolution of Chiral Diamines

Diamines with C_2-symmetry are employed extensively in the preparation of catalysts for asymmetric synthesis. Enantiomerically pure diphenylethylenediamine is one synthetically valuable example, and there are several procedures available for its preparation.[99] DPEN is also available commercially; however, its expense justifies its

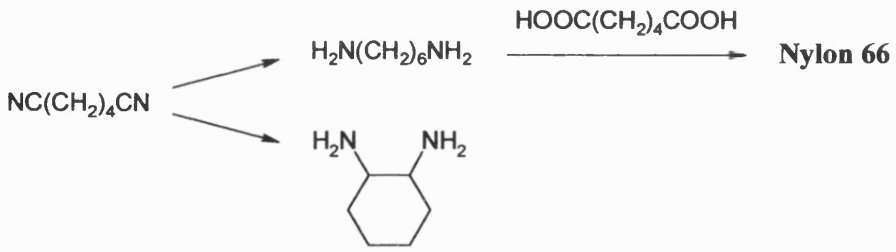
preparation from the literature protocols. Williams and Bailar described the original method for the synthesis of DPEN starting from benzaldehyde and ammonia.[99a] The reaction proceeds via 'hydrobenzamide' and 'amarine'[109] intermediates, the structures of which have been elucidated by Corey.[99b] More recently, a convenient two step synthesis has been reported by Corey. Reaction of benzil with cyclohexanone and ammonium acetate in acetic acid provides 2,2-spirocyclohexane-4,5-diaryl-2*H*-imidazole. This is converted into racemic DPEN by Birch reduction and subsequent acid hydrolysis (Scheme 54).[99c] Both of these methods were utilised for the preparation of racemic DPEN. Resolution was then achieved by fractional crystallisation using (+)-tartaric acid[99d] for (1*S*,2*S*)-(-)-DPEN and (+)-mandelic acid[100] for (1*R*,2*R*)-(+)-DPEN.



Scheme 54. Preparation of racemic diphenylethylenediamine.

Another synthetically useful diamine is 1,2-diaminocyclohexane (CYDN). As a by-product of the hydrogenation of adiponitrile[101] (Scheme 55), CYDN is available commercially as a mixture of racemic *trans*- and *cis*-isomers and is relatively inexpensive. Enantiomerically pure *trans*-CYDN has most notably been used by Jacobsen in the preparation of a highly enantioselective olefin epoxidation catalyst. As part of the optimisation procedure for the synthesis of the catalyst, Jacobsen developed

an improved method for the resolution of CYDN using the commercially available isomeric mixture.[102] Thus, using this method, several hundred grams of 1*R*,2*R*-(-)-CYDN was isolated as the mono(+)-tartrate salt. Liberation and purification of 1*R*,2*R*-(-)-CYDN by standard 'free-basing' procedures proved to be problematic because of its high solubility in water. However, it was found that liberation was best effected by the direct addition of concentrated potassium hydroxide solution to the tartrate salt. This produces a biphasic mixture in which the diamine constitutes the upper layer. Rapid removal of this layer is essential because precipitation of the potassium salt of tartaric acid occurs after just a few minutes. Distillation of the crude (wet) material from potassium hydroxide provided 1*R*,2*R*-(-)-CYDN with an acceptable specific rotation and melting point. An alternative work-up procedure is available for the isolation of CYDN, however, it is somewhat more complicated than that discussed above.[103]



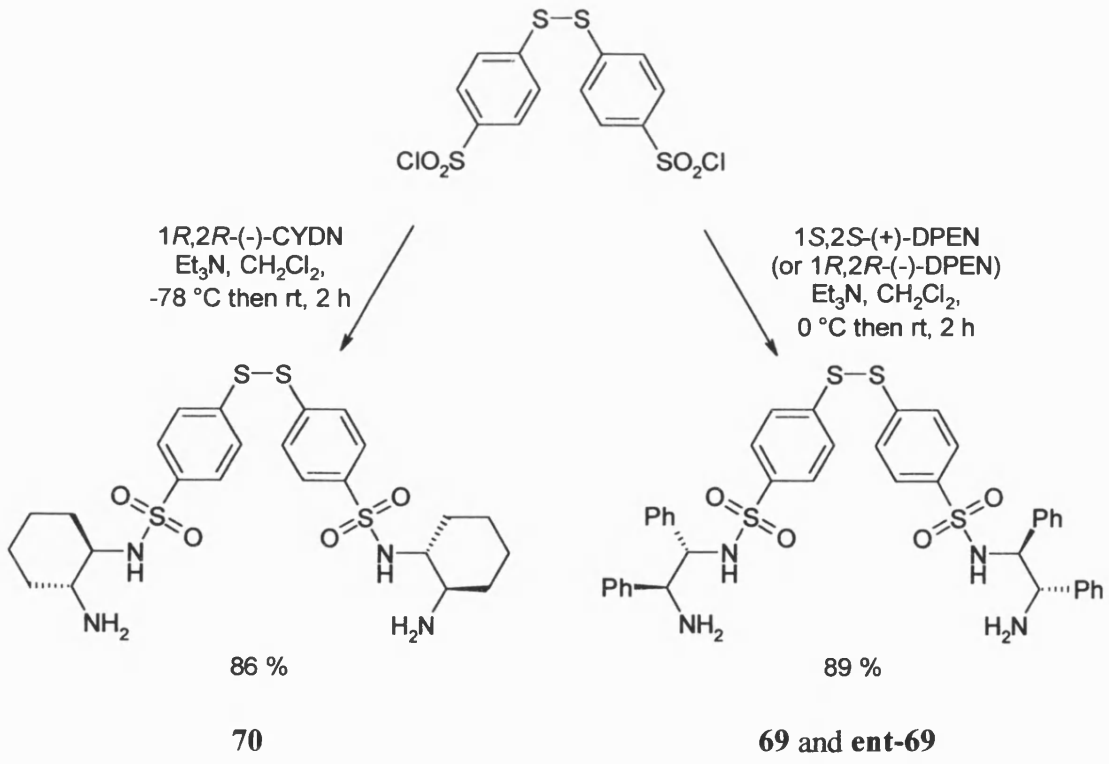
***cis*- and *trans*-CYDN**

Scheme 55. Commercial source of 1,2-Diaminocyclohexane.

Coupling of Sulfonyl Chloride 68 with Enantiomerically Pure Diamines

Addition of sulfonyl chloride **68** to a solution of 1*S*,2*S*-(+)-DPEN, 1*R*,2*R*-(+)-DPEN or 1*R*,2*R*-(-)-CYDN in dichloromethane/triethylamine (10:1) afforded sulfonamides **69**, **ent-69** and **70** respectively (Scheme 56). Purification by column chromatography gave enantiomers **69** and **ent-69** in high yield (89 – 92 %). Analysis of the ^{1}H NMR spectra confirms two different environments for benzylic protons; this is represented by two

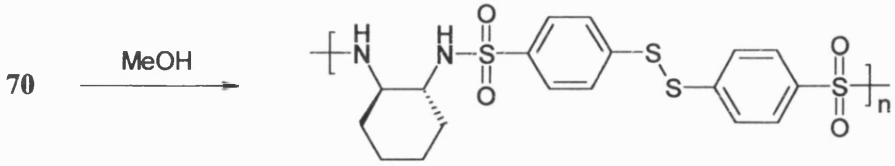
doublets in AB formation. The infrared spectra contain broad bands at approximately 3300 cm^{-1} most likely due to sulfonamide N-H stretching. Purification of compound **70** using column chromatography was more difficult to achieve than for the DPEN based sulfonamides. Here, separation from the other components of the reaction mixture (essentially Et_3NHCl, Et_3N and CYDN) required the use of a relatively polar solvent system (CH_2Cl_2/MeOH – 5:1), in which sulfonamide **70** demonstrated limited stabiiity. On a small scale, purification was possible providing that the column chromatography was performed quickly. As for enantiomers **69** and **ent-69**, two distinct C*-H environments (where C* denotes a stereogenic carbon) are visible in the ^1H NMR spectrum, and the infrared spectrum contains bands which may be assigned to sulfonamide N-H stretching.



Scheme 56. Preparation of sulfonamide ligand precursors.

On a large scale (>5 g) purification by column chromatography was unsuccessful. Several attempts to isolate compound **70** resulted only in a mixture of the desired

product and triethylamine or triethylammonium chloride. In addition to this, significant amounts of an unidentified material precipitated from the methanolic column fractions upon standing. Analysis of the characterisation data collected for this compound indicates that it is most likely an oligomer or polymer (Scheme 57). Also, the insolubility of this compound in all common solvents apart from DMSO is further evidence of a polymeric structure. The ^{1}H NMR spectrum exhibits broad resonances with an 8:10 ratio of aromatic protons to alkyl protons; resonances from two distinct C*-H environments are absent. The electrospray mass spectrum displays fragment ions which are common to the mass spectrum of sulfonamide **70**. Microanalysis gives a carbon, hydrogen, nitrogen ratio of 18:21:2, which is consistent with that of the repeating unit in Scheme 57.



Scheme 57. Suggested degradation product of sulfonamide **70**.

The structure shown is just one possibility based on the characterisation data obtained. Superficially, its formation requires nucleophilic attack of a free primary amine on the sulfonamide functionality. This is not a general reaction of sulfonamides and seems unlikely. However, attack of the free primary amine on the disulfide bond is more likely. Ionic scission of disulfide bonds with ammonia and amines to yield the corresponding sulfenamide is known (Scheme 58).[104]

Scheme 58. Sulfenamide formation via ionic scission of a disulfide bond.

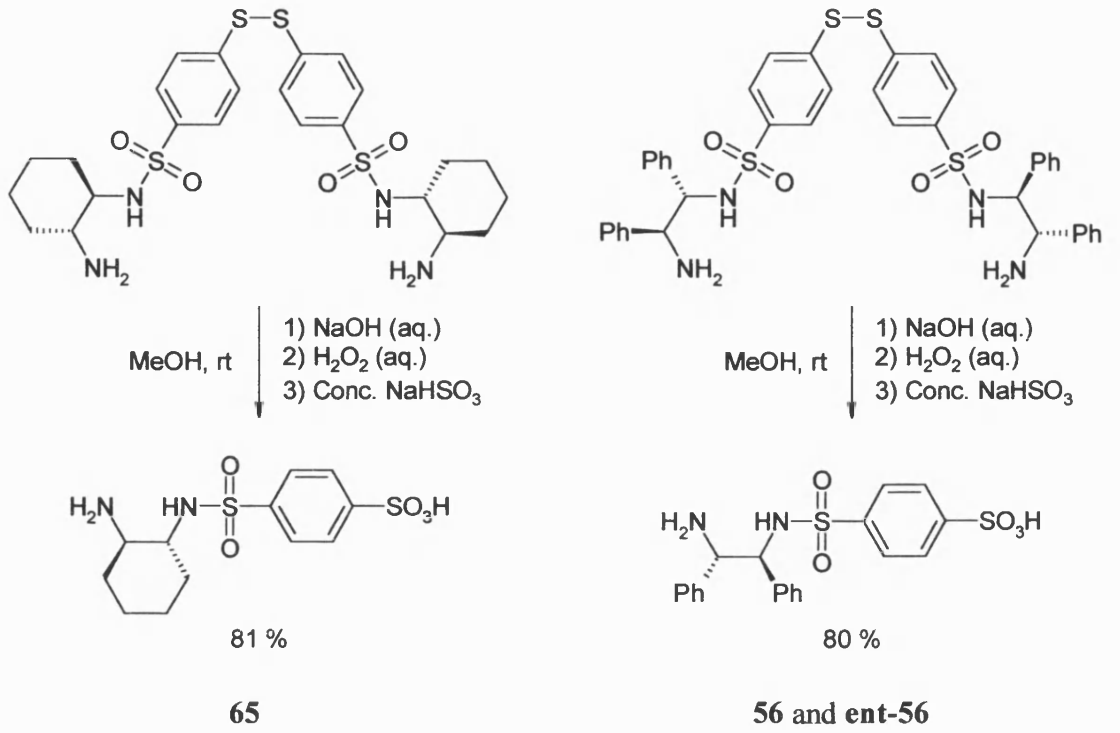
The large-scale synthesis of compound **70** was achieved by using a different work-up procedure. Instead of using column chromatography, a series of extractions was used to remove the major impurities. An initial aqueous extraction removed residual CYDN and the majority of the triethylammonium chloride. A second extraction using sodium hydrogencarbonate solution converted any remaining triethylammonium chloride into triethylamine, which was then removed under reduced pressure. Using this method sulfonamide **70** was easily prepared on a 25 g scale.

There is a good deal of stereochemical and kinetic data which suggest that nucleophilic substitution of sulfonyl chlorides proceeds via an S_N2-like mechanism with backside attack.[105] For example, Sabol and Andersen demonstrated that isotopically labelled, enantiomerically pure sulfonate esters underwent inversion of configuration when reacted with a Grignard reagent (Scheme 59).

Scheme 59. Nucleophilic substitution of a chiral sulfonate ester (O* = ^{18}O, R = menthyl).

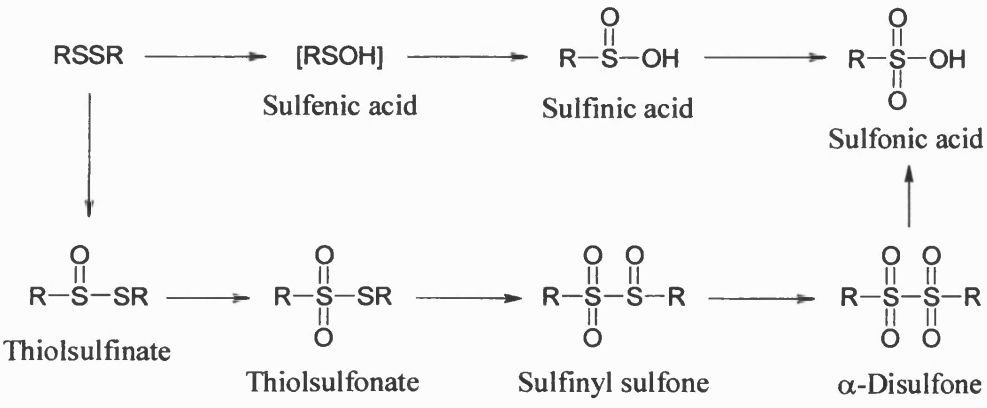
Oxidation of the Disulfide Bond

Treatment of sulfonamides **69**, **ent-69** and **70** with hydrogen peroxide solution under basic conditions effected oxidation of the disulfide bond providing sulfonic acid ligands **56**, **ent-56** and **65** respectively, as the sodium salts. Precipitation of the ligands from the reaction mixture was brought about by the addition of sodium hydrogensulfite solution; each ligand was then isolated in high yield (Scheme 60). These compounds are colourless solids that decompose before melting. The infrared spectra contain bands at approximately 1600 and 3100 cm^{-1} revealing the presence of an NH_3^+ functionality. Hence, this confirms that these ligands exist as the internal salt or 'zwitterion'.



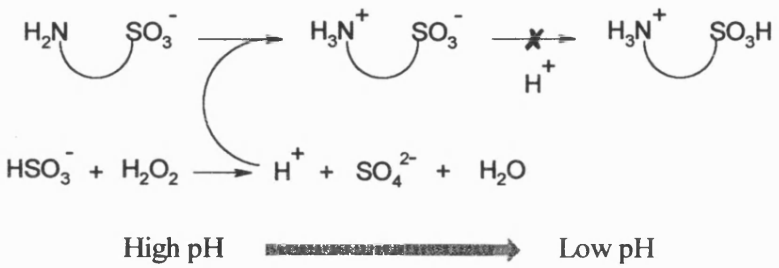
Scheme 60. Disulfide oxidation.

The oxidation of disulfides ultimately leads to sulfonic acids, however, the oxidation process proceeds through several intermediates (Scheme 61).[106] In the presence of aqueous sodium hydroxide, cleavage of the disulfide bond occurs making the top sequence more likely. Nevertheless, interplay between the top and bottom sequence may occur through a process of bond cleavage and recombination.



Scheme 61. Intermediates in the oxidation of disulfides.

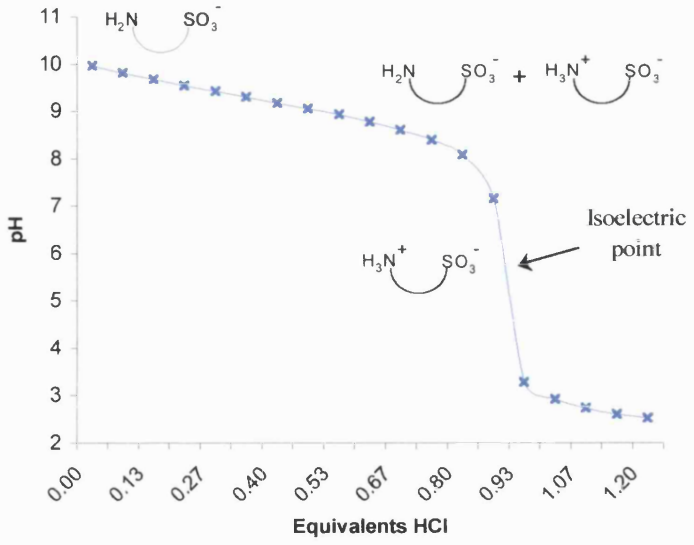
Precipitation of the ligand from the reaction mixture was unexpected and fortunate. The primary function of the sodium hydrogensulfite solution was to destroy residual hydrogen peroxide.[107] However, a change in pH (alkaline to acidic) also accompanied the addition, which allowed protonation of the amine nitrogen, therefore forming the internal salt of the ligand. In the zwitterionic form these ligands exhibit a low solubility in most common solvents, hence their precipitation from the reaction mixture. The pKa values of arenesulfonic acids[108] are usually in the range of -6 to -7, therefore further protonation of the ligand (i.e. protonation of the sulfonate group) to provide a water-soluble cationic species did not occur under the reaction conditions (Scheme 62).



Scheme 62. Precipitation of ligands as 'zwitterions' on the addition of sodium hydrogen sulfite.

Titration of a solution of ligand **65** (initially dissolved with one equivalent of base) with hydrochloric acid allowed a rough calculation of the isoelectric point (Graph 3). At approximately pH 5.5 this ligand is entirely neutral. Above this pH, a proportion of the ligand will be ionised and therefore soluble in the reaction mixture. Hence, it follows that ligand yields can be maximised by ensuring that the solution pH is below pH 6.

The oxidation method described was suitable for direct scale-up and allowed the preparation of more than 23 g of aminosulfonamide ligand **65**.

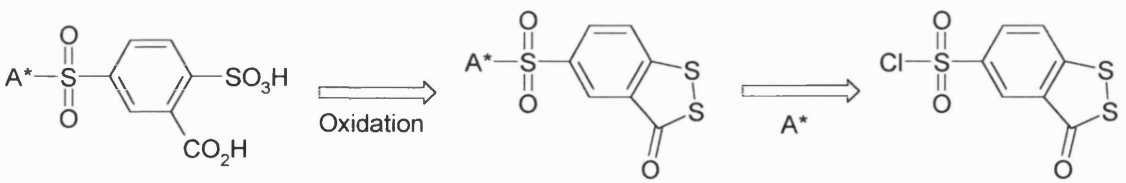


Graph 3. Determination of the isoelectric point of ligand **65**.

Synthesis of Ligand 66

The sodium or potassium salts of ligands **56** and **65** demonstrate sufficient water-solubility for use in aqueous catalysis. The next step was to investigate the synthesis of ligand **66**, which incorporates an additional polar functionality in the form of a carboxylate group. With its higher polarity, this ligand may have greater potential than ligands **56** or **65** in supported liquid phase catalysis.

The retrosynthetic analysis for structure **66** is given in Scheme 63. The synthesis would begin with the chlorosulfonation of commercially available 3*H*-1,2-benzodithiol-3-one to form sulfonyl chloride **71**.

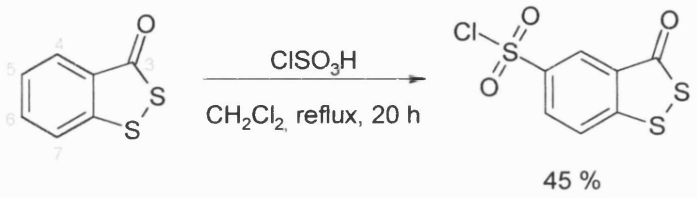


71

Scheme 63. Retrosynthetic analysis 3 (A* = chiral diamine).

Synthesis of Sulfonyl Chloride 71

The synthesis of compound **71** was achieved via the reaction of 3*H*-1,2-benzodithiol-3-one with an excess of chlorosulfonic acid at reflux (Scheme 64). The optimum reaction time was found to be approximately 20-hours, with chlorosulfonic acid and 3*H*-1,2-benzodithiol-3-one concentrations of 2 moldm^{-3} and 0.2 moldm^{-3} respectively. Longer reaction times and higher $ClSO_3H$ concentrations produced multi-substituted products. The modest yield of the reaction (45 %) may be due to decomposition of the sulfonyl chloride functionality under the hydrolytic work-up conditions.



Scheme 64. Chlorosulfonation of 3*H*-1,2-benzodithiol-3-one.

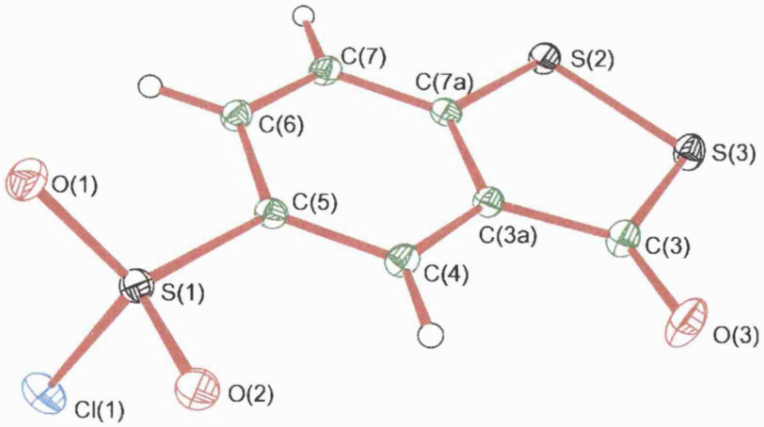


Figure 16. ORTEP representation of the crystal structure of sulfonyl chloride **71**.

NMR data alone was not sufficient to allow confirmation of the structure of the isolated product. After consideration of the ^{1}H NMR spectrum, substitution at C-4 or C-7 could be ruled out. Electrophilic substitution at C-5 or C-6 would give rise to similar ^{1}H NMR spectra. Therefore, the structure was elucidated by X-ray crystallography; this

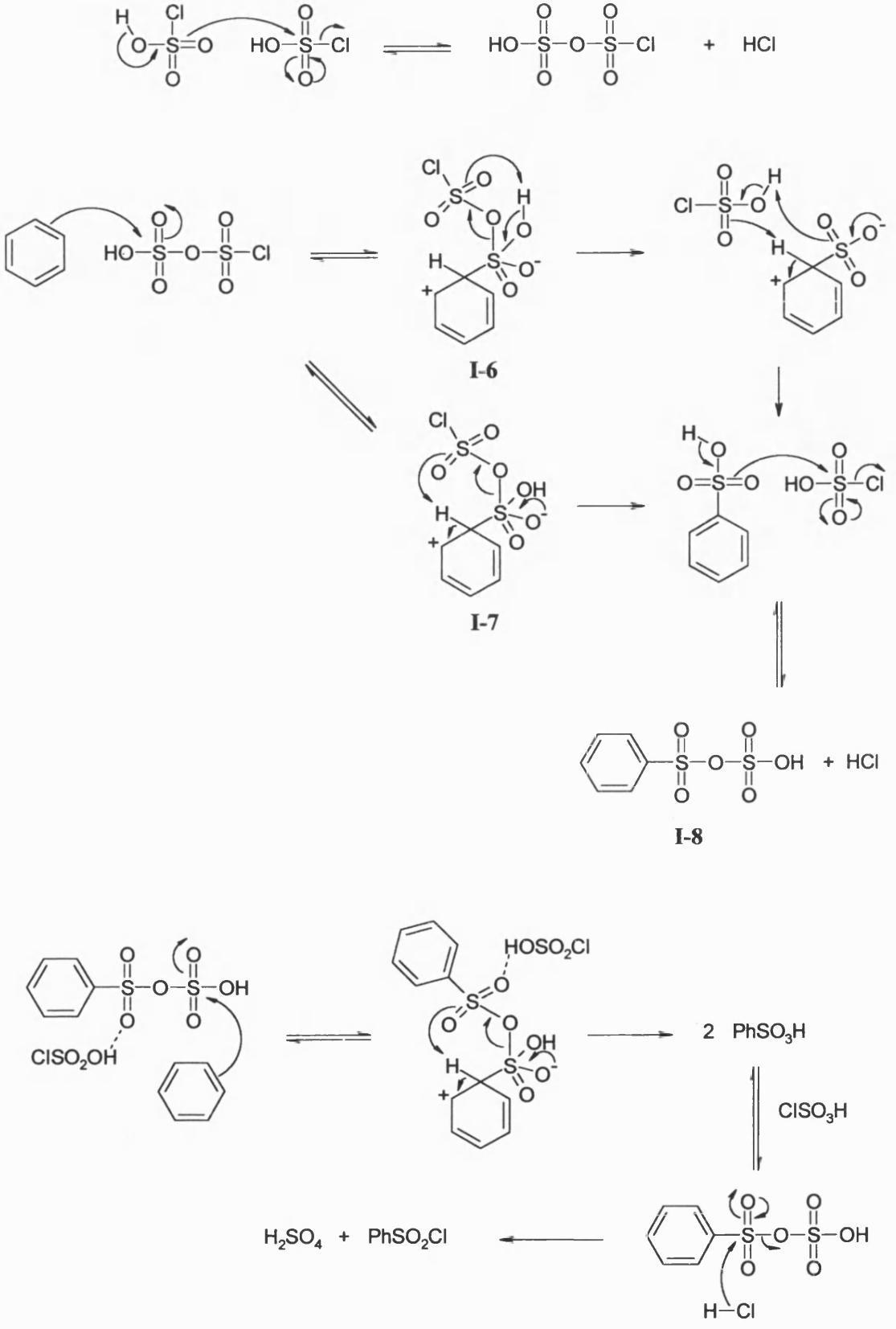
established a C-5 position for the sulfonyl chloride group (Figure 16). This result was expected considering the individual directing effects of the ring substituents. The carbonyl group has a *meta*-directing influence on aromatic electrophilic substitution whilst the sulfur group has a *para*- and *ortho*-directing effect.

There is little information regarding the mechanism of chlorosulfonation with chlorosulfonic acid. However, arenesulfonyl chlorides are thought to be secondary products in the reaction of $ClSO_3H$ with aromatic substrates. The initial products in this reaction are arenesulfonic acids. Cerfontain and van Albada studied the kinetics of aromatic sulfonation with chlorosulfonic acid and were able to derive some mechanistic data using their results.[110] Using benzene as a substrate and dichloromethane as a solvent, the mechanism of sulfonation is thought to proceed as in Scheme 65b. The initial sulfonation of benzene probably involves ClS_2O_6H as the attacking electrophile and proceeds through σ-complexes **I-6** or **I-7**. The low polarity of the solvent excludes the intermediacy of charged species. The benzenesulfonic acid thus formed may then combine with chlorosulfonic acid to provide intermediate **I-8**; this is proposed to be the major sulfonating entity in the reaction mixture when hydrogen bonded to an additional $ClSO_3H$ molecule. With a deficiency of chlorosulfonic acid, arenesulfonic acids are the primary and main products. With an excess of $ClSO_3H$, arenesulfonyl chlorides are formed, possibly as indicated in Scheme 65b. As this reaction is an equilibrium, a considerable excess of $ClSO_3H$ is required to maximise the yield of the desired sulfonyl chloride. The overall process of chlorosulfonation may be summarised as in Scheme 65a.

$$RH + ClSO_3H \longrightarrow RSO_3H + HCl$$

$$RSO_3H + ClSO_3H \rightleftharpoons RSO_2Cl + H_2SO_4$$

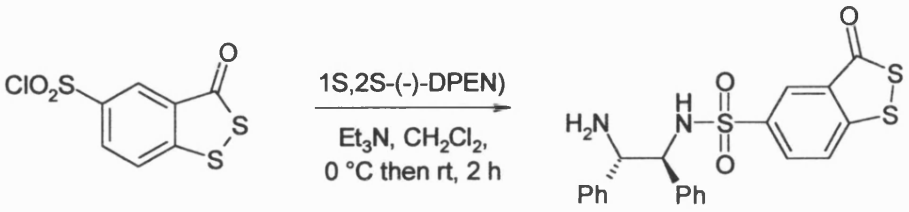
Scheme 65a. Summary of chlorosulfonation process.



Scheme 65b. Detailed mechanism of the sulfonation of benzene with chlorosulfonic acid in dichloromethane as proposed by Cerfontain and van Albada.

Coupling of Sulfonyl Chloride 71 with Enatiomerically Pure DPEN

Addition of 3-Oxo-3*H*-1,2-benzodithiole-5-sulfonyl chloride **71** to a solution of 1*S*,2*S*-(+)-DPEN in dichloromethane/triethylamine afforded sulfonamide **72** (Scheme 66). Purification was then achieved using column chromatography and provided the desired compound in high yield.



83 %

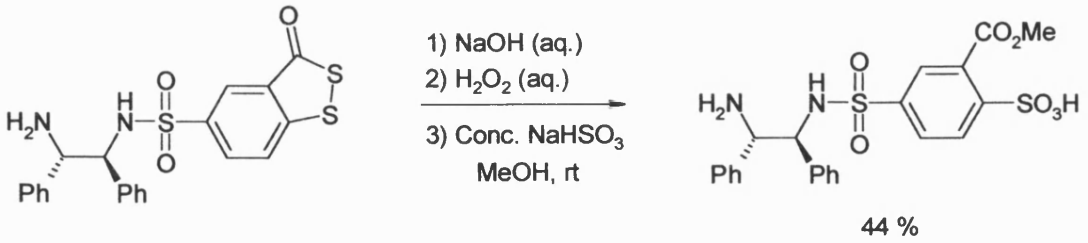
72

Scheme 66. Sulfonamide formation.

Once again, notable in the ^{1}H NMR spectrum was the characteristic pair of AB doublets. These indicate different environments for benzylic protons and therefore confirm that only a single amine group of DPEN has undergone sulfonamide formation.

Oxidation of the Disulfide Bond

The disulfide bond of sulfonamide **72** was oxidised using the previously described method. Unexpectedly, diacid **66** (as the free acid) was not obtained. Instead, methyl ester **73** was isolated (Scheme 67). It seems that the acidic conditions of the work-up promoted esterification of the carboxylic acid functionality with the alcohol solvent. Thus, insoluble ester **73** was collected and washed with a variety of solvents in order to remove inorganic residues and other impurities. In retrospect, this unanticipated reaction was fortunate since the desired diacid **66** would have proved more difficult to isolate and purify because of its higher solubility in polar solvents. Saponification of ester **73** to diacid **66** would be a straightforward and relatively 'clean' reaction.



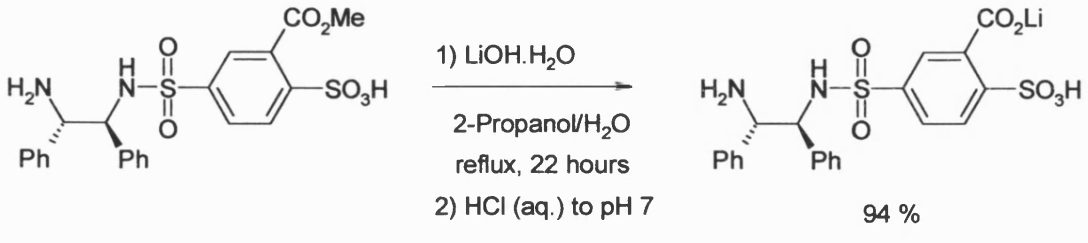
73

Scheme 67. Disulfide oxidation.

The moderate yield of this reaction is probably a consequence of the reversible nature of the Fischer esterification step. The ratio of ester **73** to diacid **66** is dependent upon the composition of the reaction solvent. Ester formation will be maximised when the ratio of methanol to water in the reaction mixture is greatest. Since the reagents used in this reaction are aqueous solutions, the yield of ester **73** will be compromised.

Ester Hydrolysis

Saponification of methyl ester **73** was achieved using lithium hydroxide monohydrate in a 2-propanol/water (98:2) mixture at reflux. Lithium salt **66** precipitated upon the neutralisation of the reaction mixture and was isolated in high yield (Scheme 68).



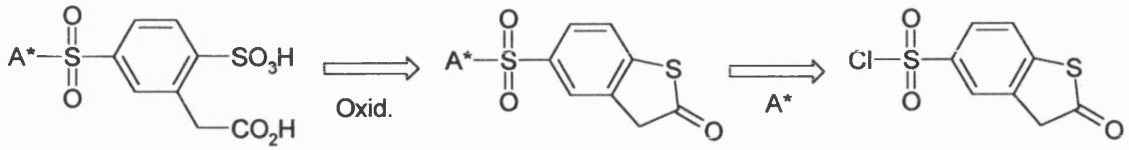
66

Scheme 68. Ester saponification.

Attempted Synthesis of an Additional Polar Aminosulfonamide Ligand

The retrosynthetic route to an analogue of ligand **66** is given in Scheme 69. This synthesis would allow the incorporation of the carboxylic acid functionality in the

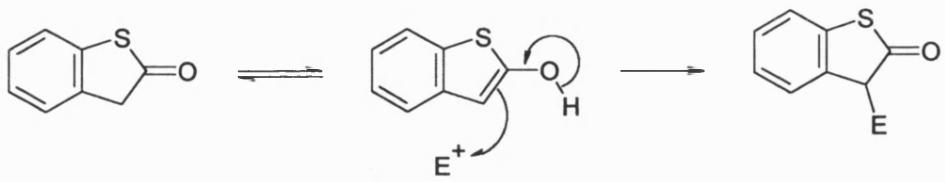
benzylic position; this is in contrast to ligand **66** where the carboxylate group is a direct substituent of the aromatic ring. A comparison of the efficacy of these ligands would provide some information on ring substituent effects and therefore allow the tailoring of future ligands.



74

Scheme 69. Retrosynthetic analysis 4 (A* = chiral diamine).

At the outset of this synthesis some possible problems were envisaged, primarily regarding the synthesis of compound **74**. A method for the preparation of sulfonyl chloride **74** involves the electrophilic aromatic substitution of benzo[*b*]thiophen-2(3*H*)-one **75** using chlorosulfonic acid; this approach had previously been used for synthesis of sulfonyl chloride **71** starting from 3*H*-1,2-benzodithiol-3-one. Whilst these starting substrates are similar in structure, their chemistry may differ considerably owing to the presence of an α-CH_2 group in benzo[*b*]thiophen-2(3*H*)-one. Under the acidic reaction conditions, the *enol*-tautomer of this substrate may exist to a significant extent. Therefore, an electrophile would be more likely to attack the α-position rather than the aromatic ring (Scheme 70). Nevertheless, the synthesis of **74** was attempted.

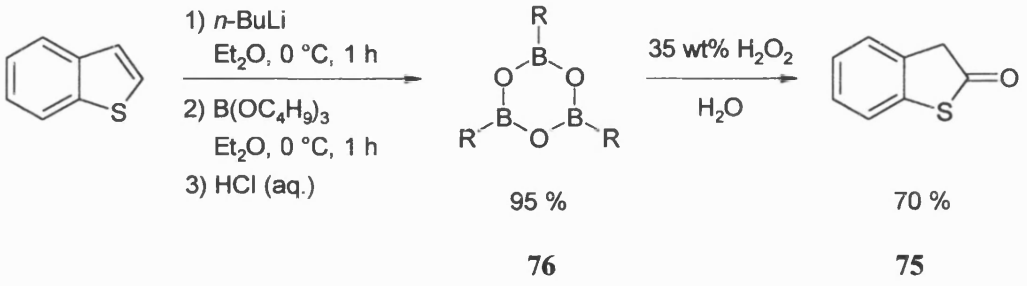


75

Scheme 70. α-Substitution of benzo[*b*]thiophen-2(3*H*)-one.

Preparation of Thiolactone 75

Thioester **75** was prepared using the two-stage method reported by Dickinson and Iddon, which utilises commercially available benzo[*b*]thiophene as the starting material.[111a] Thus, treatment of benzo[*b*]thiophene with *n*-butyllithium provided 2-lithiobenzothiophene. Metallation occurs exclusively at the C-2 position due to the influence of the neighbouring sulfur atom. Reaction of the 2-lithio species with n-butyl borate followed by hydrolysis of the product with aqueous acid gave cyclotriboroxane **76** in high yield. This product arises from the dehydration of the intermediate boronic acid during work-up. Treatment of compound **76** with hydrogen peroxide gave thiolactone **75** in respectable yield (Scheme 71).



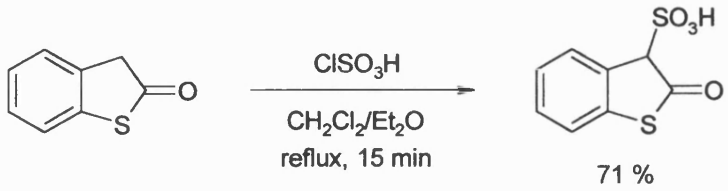
Scheme 71. Synthesis of benzo[*b*]thiophen-2(3*H*)-one, (R = 2-benzo[*b*]thienyl).

The NMR and infrared spectra contained no evidence of the *enol*-tautomer of compound **75**. However, the *keto*-tautomer was evidenced by a strong band at 1716cm^{-1} (C=O) in the infrared spectrum and also by resonances which may be assigned to a CH_2 group in the ^{1}H and ^{13}C NMR spectra.

Attempted Synthesis of Sulfonyl Chloride 74

Reaction of benzo[*b*]thiophen-2(3*H*)-one **75** with an excess of chlorosulfonic acid at reflux produced a mixture of products. Since there were concerns about the regioselectivity of this reaction, no attempts were made to try and optimise reaction conditions in order to obtain a single product. Instead, the reaction was repeated with a

deficiency of chlorosulfonic acid. Despite the fact that this would produce the sulfonic acid derivative, it would at least allow the initial position of electrophilic substitution to be established. As suspected, initial substitution occurred at the α-position and not in the aromatic ring, therefore yielding sulfonic acid **77**; this is the product resulting from the reaction of the *enol*-tautomer of thioester **75** (Scheme 72).



71 %

77

Scheme 72. Reaction of chlorosulfonic acid with benzo[*b*]thiophen-2(3*H*)-one.

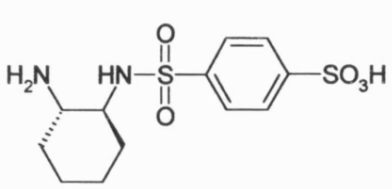
2.2.3 Summary

- An improved method for the synthesis of TPPDS (disodium 3-[phenyl(3-sulfonatophenyl)phosphino]benzenesulfonate) has been developed. This represents a quick and reliable means to a water-soluble phosphine with essentially no phosphine oxide formation.
- Polar analogues of Noyori's (1*S*,2*S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylene diamine and Knochel's (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diaminocyclohexane have been synthesised. Ligands **56**, **ent-56**, and **65** were prepared from cheap and readily available sulfanilic acid using a four-step procedure, and were obtained with an average overall yield of 24 %. Ligand **66** containing an additional carboxylate functionality was also synthesised in four steps with an overall yield of 15 %.
- A method for the large-scale synthesis of ligand **65** has been developed.

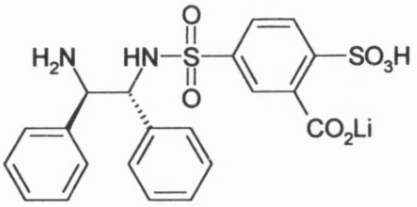
- Chlorosulfonation of benzo[*b*]thiophen-2(3*H*)-one was unsuccessful owing to the tautomeric nature of the starting ketone.

2.2.4 Future Work

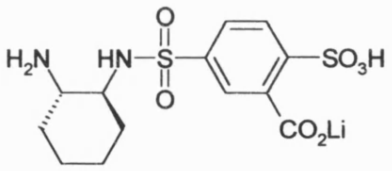
Figure 17 shows target structures that may also be of interest. Ligands **ent-65** and **ent-66** are the enantiomers of ligands **65** and **66** respectively. Their preparation should be straightforward using the procedures described in Section 2.2.2.2.



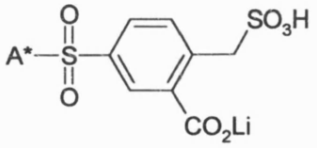
ent-65



ent-66



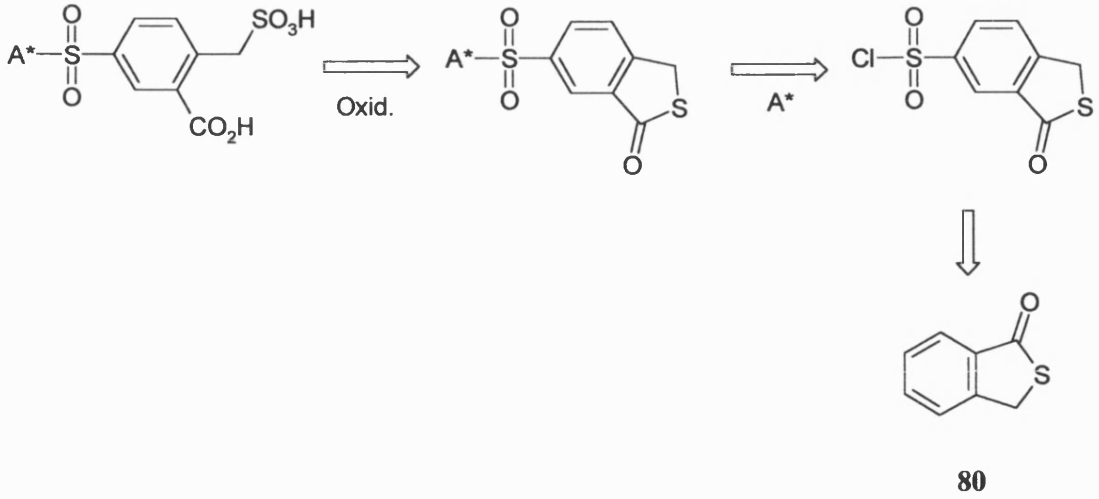
78



79

Figure 17. Future target molecules (A* = enantiomerically pure DPEN or CYDN)

Target ligand **78** should be available using a similar procedure to that described for the synthesis of compound **66**. The substitution of DPEN for CYDN ought to provide a ligand with an even higher water-solubility. Finally, targets of type **79** might possibly be prepared starting from benzo[*c*]thiophene-1(3*H*)-one **80** (Scheme 73). Unlike benzo[*b*]thiophen-2(3*H*)-one **75**, this starting material would not have an *enol*-tautomer and therefore the introduction of the sulfonyl chloride functionality using chlorosulfonic acid should pose no problems.



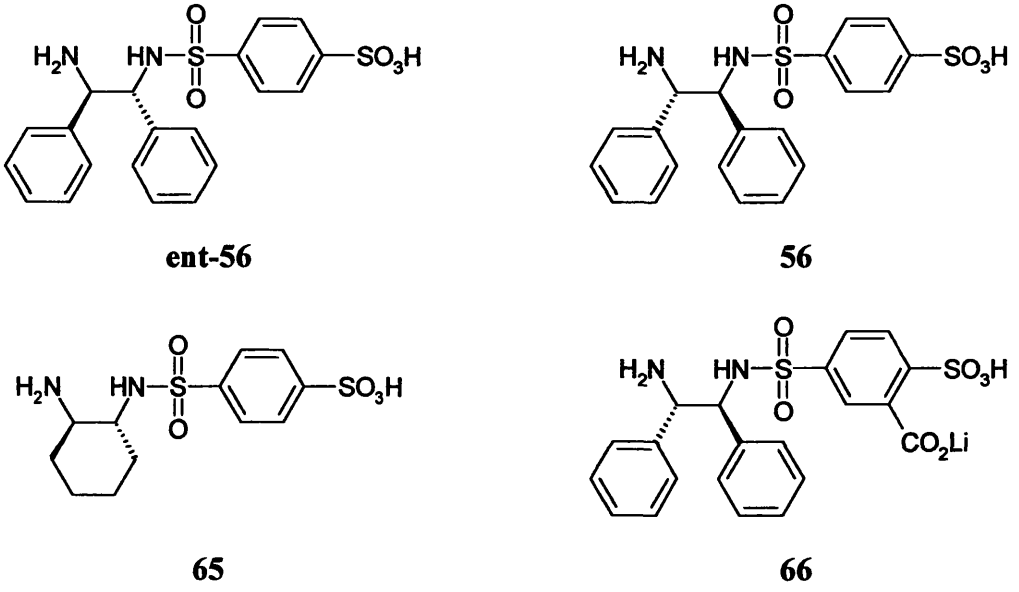
80

Scheme 73. Retrosynthetic analysis 5 (A* = enantiomerically pure DPEN or CYDN).

2.3 Application of Polar Ligands in the Transfer Reduction of Aromatic Ketones Under Homogeneous Conditions

Having synthesised a variety of polar ligands, the next step of the project was to demonstrate the utility of these in the transfer hydrogenation of simple aromatic ketones. As discussed in Chapter 1, complexes of ruthenium have proved most effective for the purpose of transfer reduction, followed by rhodium and iridium catalysts. Also, it was apparent that Ru(II)/phosphine complexes were generally inferior to Ru(II)/tosylated diamine or Ru(II)/amino alcohol complexes. For this reason, the initial idea of employing sulfonated phosphines for the synthesis of polar transfer hydrogenation catalysts was not pursued. It should be noted, however, that Ru(II)/TPPTS complexes have been utilised for the *direct* hydrogenation of C=O bonds.[81]

This section therefore focuses on the use of polar aminosulfonamide ligands **56**, **ent-56**, **65** and **66** (Figure 18) in combination with ruthenium, rhodium and iridium for transfer reduction under homogeneous conditions. A system such as this would allow the true potential of the polar ligands/catalysts to be established before further application to biphasic and perhaps supported liquid phase systems.



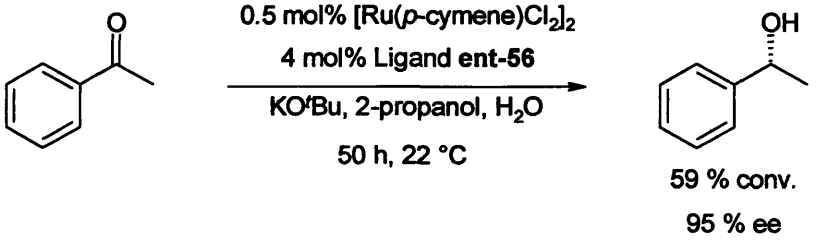
ent-56 **56**

65 **66**

Figure 18. Polar aminosulfonamide ligands for use in asymmetric transfer hydrogenation.

2.3.1 Ruthenium-Catalysed Asymmetric Transfer Hydrogenation

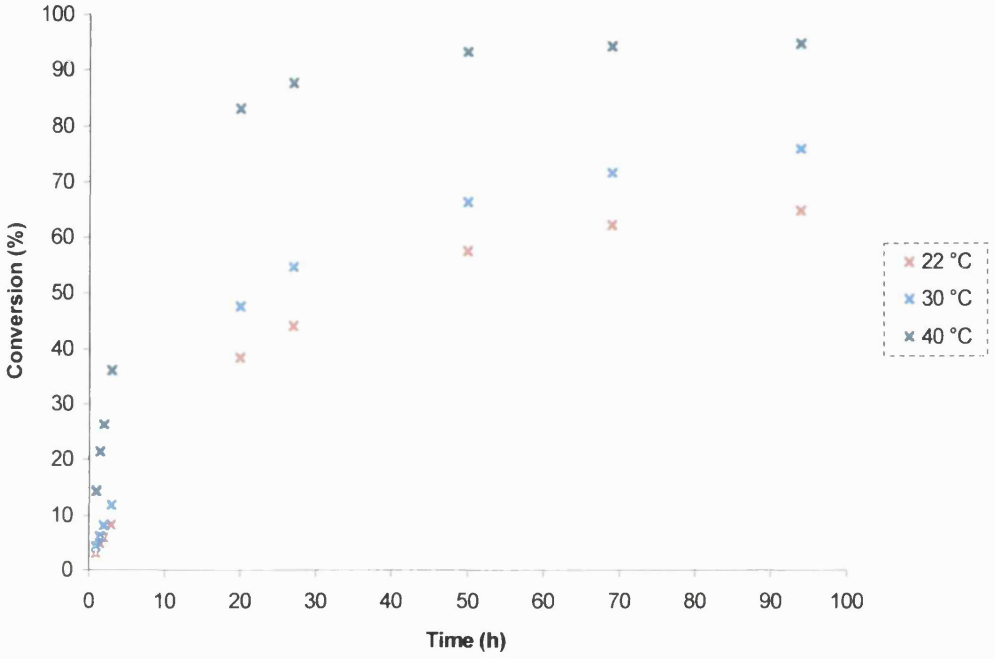
The transfer hydrogenation method used to investigate the efficacy of the polar aminosulfonamide ligands is given in Scheme 74. This procedure closely resembles that used by Noyori for transfer reductions involving tosylated diamine ligands.[62a] Thus, an enantiomerically pure ruthenium complex was prepared from the reaction of $[RuCl_2(p\text{-cymene})]_2$ and aminosulfonamide ligand **ent-56** in the presence of base (Ru atom:ligand:base 1:4:4) at 40 °C for 2 hours; this was then used immediately without isolation. When a 0.15 M solution of acetophenone (S/C = 100) in 2-propanol/water (12:1) was combined with the catalyst solution in the presence of additional base, (*R*)-1-phenylethanol was obtained. After a 50-hour period at room temperature, a 59 % conversion was achieved with an enantiomeric excess of 95 %.



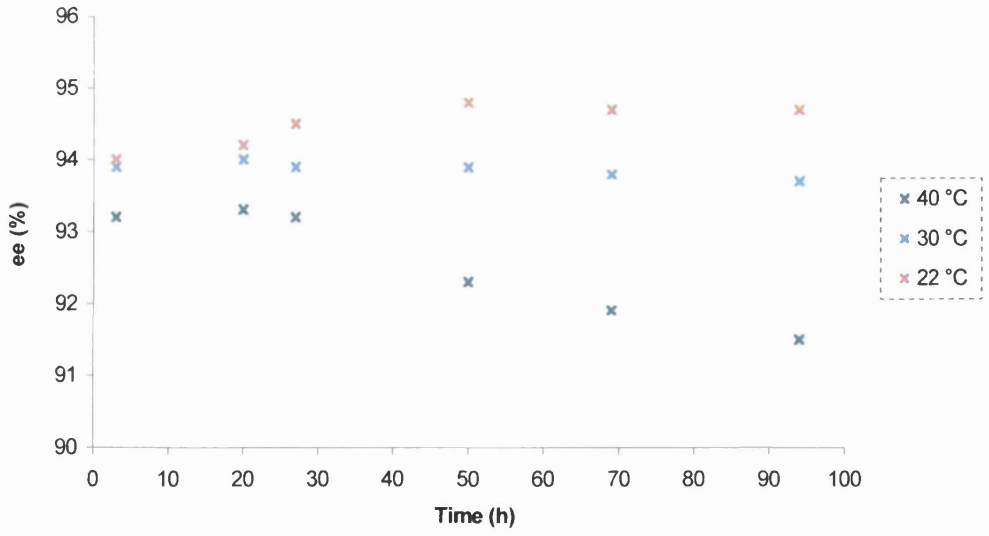
Scheme 74. Reaction conditions for Ru-catalysed asymmetric transfer reduction.

This initial result was satisfactory in terms of enantiomeric excess. However, the rate of conversion of acetophenone to 1-phenylethanol was significantly lower than that of Noyori's Ru(II)-TsDPEN system (95 % conversion, 97 % ee in 15 hours). Therefore, the effect of temperature on the reaction was investigated. Graphs 4 and 5 display the results obtained when the reaction depicted in Scheme 74 was run at 22, 30 and 40 °C. As expected, an increase in reaction temperature produced an increase in the rate of conversion of acetophenone into 1-phenylethanol (Graph 4). After 27 hours at 40 °C the reaction had almost reached completion; 88 % of the acetophenone had been reduced. Graph 5 shows the variation of enantiomeric excess with time for each reaction.

Noticeable is the detrimental effect of a higher reaction temperature. The difference in ee for the reaction at 22 °C and that at 40 °C is more than 3 % after 94 hours. For the reaction at 40 °C, a sudden drop in ee is also visible between 27 and 50 hours. This coincides with the reaction reaching equilibrium, and demonstrates that unnecessary exposure of the catalyst to reaction mixture will compromise the enantiomeric excess.



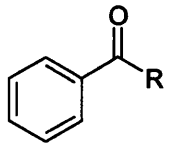
Graph 4. Effect of reaction temperature on the rate of reduction of acetophenone.



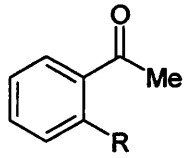
Graph 5. Effect of reaction temperature on enantiomeric excess.

The performance of aminosulfonamides **56**, **ent-56** and **65** in the asymmetric transfer reduction of acetophenone and other substrates (Figure 19 & 'fold-out' sheet p154) was also determined under the described experimental conditions (Scheme 74); the results are given in Table 7. As expected, ligands **56** and **ent-56** give near identical results in terms of conversion and enantiomeric excess for the reduction of acetophenone. Of course, the product alcohols are of opposite configuration. Comparison of the results obtained for ligands **56** and **65** shows that there is little difference in their general effectiveness.

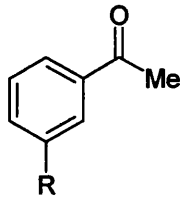
The structure and electronic properties of the ketone substrate had a significant effect on the outcome of the reaction. Acetophenones with electron withdrawing substituents (e.g. **81k** & **81i**) were reduced rapidly to the corresponding alcohol, whilst substrates bearing electron donating substituents (e.g. **81n**) were reduced more slowly. Adkins and co-workers have measured the relative oxidation potentials of various ketones, and these may be used to gauge the ease with which a particular substrate is reduced.[55] *p*-Methoxyacetophenone **81n** has a lower oxidation potential than acetophenone **81a** and is therefore more difficult to reduce.



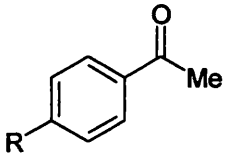
81a: R = Me, **81b**: R = Et, **81c**: R = CO_2Me



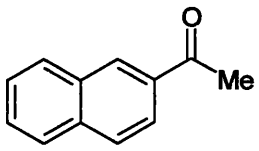
81e: R = CF_3, **81f**: R = F, **81g**: R = Cl, **81h**: R = Br



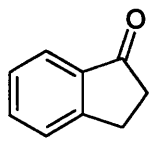
81i: R = CF_3, **81j**: R = F



81k: R = CF_3, **81l**: R = Br, **81m**: R = Cl, **81n**: R = OMe



81o



81p

Figure 19. Substrates utilised in transfer hydrogenation experiments.

Ketone	Ligand	Reaction Time (h)	Conv. (%)	ee (%)	Configuration[119]
81a	**ent-56**	50	59	95	*R*
81a	**56**	41	58	96	*S*
81a	**65**	51	54	91	*R*
81k	**56**	4	100	81	*S*
81k	**65**	4	100	88	*R*
81i	**56**	24	90	87	*S*
81i	**65**	24	91	81	*R*
81e	**56**	18	10	24	*S*
81e	**65**	18	18	55	*R*
81n	**56**	42	31	91	*S*
81n	**65**	42	35	83	*R*
81o	**56**	72	94	95	*S*
81o	**65**	48	87	90	*R*
81l	**ent-56**	74	85	92	*R*
81f	**ent-56**	115	91	75	*R*
81c	**ent-56**	2	-	-	-

Table 7. Ru-catalysed asymmetric transfer hydrogenation of various aromatic ketones.

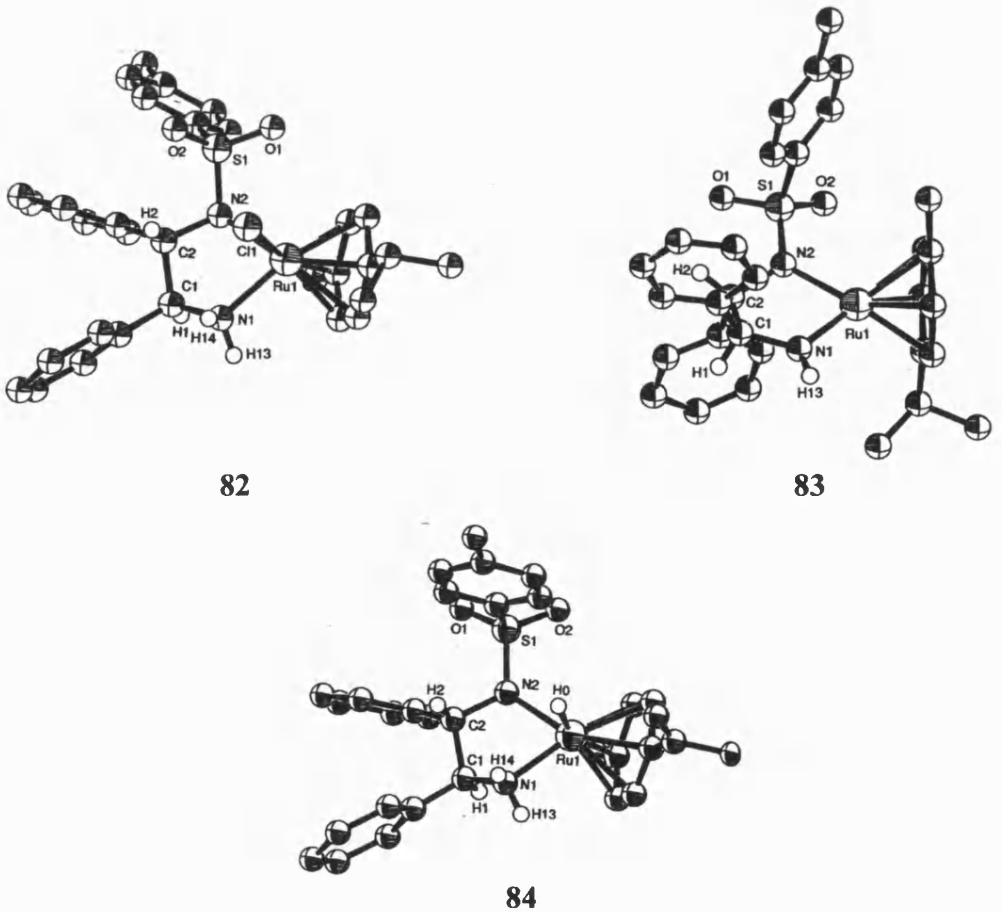
The presence of substituents in the *ortho*-position (e.g. ketones **81e** & **81f**) caused a reduction in the rate and enantioselectivity of the reaction. Conversion of α-keto ester **81c** to the corresponding alcohol, methyl mandelate, was unsuccessful. Under the conditions of the reaction, transesterification occurred yielding the isopropyl ester derivative of **81c**. In contrast, Lemaire and co-workers have reported the successful transfer reduction of methyl benzoylformate, using 2-propanol as the hydrogen donor in the presence of base. Methyl (*R*)-(-)-mandelate was obtained in >99 % enantiomeric excess (only one product detected by gas chromatography) and the conversion was quantitative after 1 hour! Under identical reaction conditions, the reduction of acetophenone took 7 days, and 1-phenylethanol was isolated with only a 67 % ee.[112]

On the whole, Ru(II) catalysts incorporating aminosulfonamides ligands **56** (or **ent-56**) and **65** perform well in transfer hydrogenation reactions. Whilst these polar catalysts

have a somewhat lower activity than that of their non-polar counterparts, their enantioselectivity remains comparable.

2.3.1.1 Reaction Mechanism

Transfer reduction involving polar aminosulfonamide ligands is likely to proceed via the metal-ligand bifunctional mechanism as proposed by Noyori.[60] This is the generally accepted mechanism for Ru(II)-catalysed transfer hydrogenation in which monotosylated diamine and β-amino alcohol ligands are used, and is supported not only by experimental data but also by the results of computer modeling studies. Extensive research by Noyori has resulted in the isolation and X-ray characterisation of the catalyst precursor **82**, the 'true' catalyst **83** and the ruthenium hydride reactive intermediate **84** (Figure 20 & Scheme 75) involved in the Ru(II)-TsDPEN system.[62f]

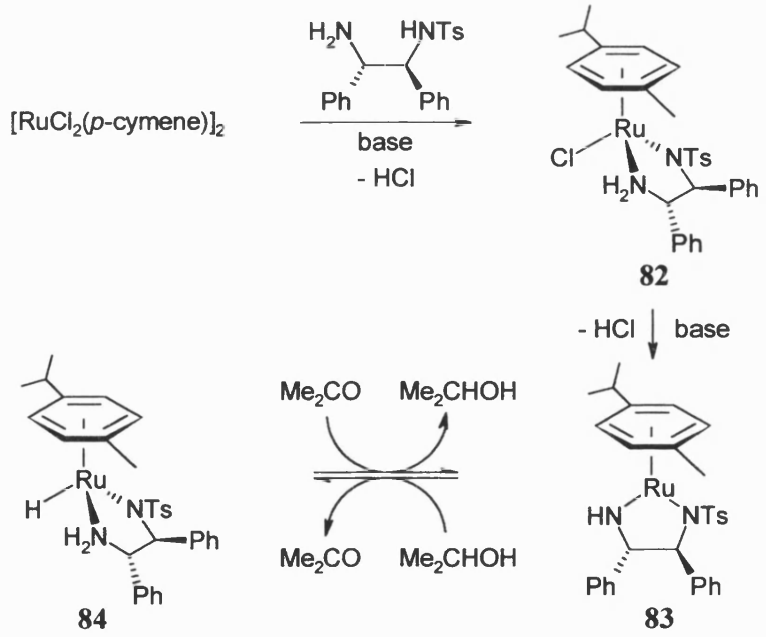


82 **83**

84

Figure 20. Molecular structures of the isolated Ru(II) complexes.

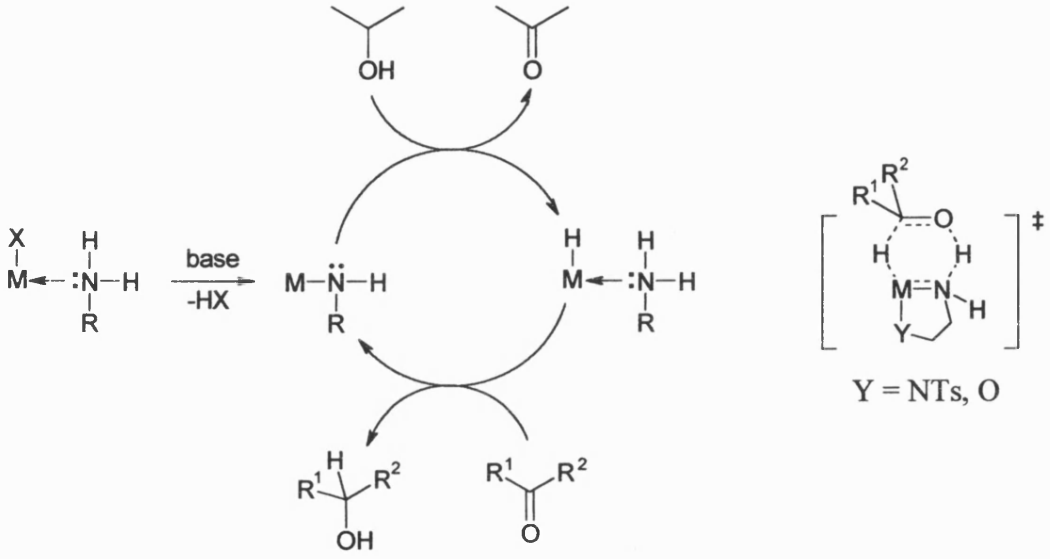
Formation of 18-electron complex **82** was achieved by reacting $[RuCl_2(p\text{-cymene})]_2$ and (*S*,*S*)-TsDPEN in the presence of base. Initial experiments, which examined the acceleration effect of various ligands on the rate of transfer reduction, revealed that a tosyl functionality in diamine ligands is essential for rate acceleration; ethylenediamine produced no rate enhancement.[56] The tosyl group serves to enhance the acidity of the remaining NH proton, thus stabilising the five-membered chelate Ru(II) complexes. Catalyst precursor **82** has acidic NH_2 protons and therefore in the presence of base (e.g. KOH) eliminates HCl thus forming the 'true' catalyst **83**. This 16-electron Ru(II) complex dehydrogenates alcohols (e.g. 2-propanol) to give the 18-electron ruthenium hydride species **84** and the corresponding carbonyl compound (e.g. acetone). Complexes **83** and **84** were able to catalyse the transfer hydrogenation of acetophenone in the absence of KOH, affording enantioselectivities comparable to those obtained with the *in situ* formed catalyst.



Scheme 75. Formation of the isolated Ru(II) complexes.

The experimental evidence along with results obtained from theoretical studies[60,67a] have led to the proposal of the general catalytic cycle in Scheme 76. Reduction of the ketone

substrate is believed to involve the concerted transfer of hydride and a proton via a six-membered cyclic transition state. In this unusual mechanism, the metal *and associated ligand* directly participate in the bond-forming and bond-breaking steps of the dehydrogenative and hydrogenative processes. This is in contrast to the majority of transition metal-catalysed reactions, where the main role of the organic ligands is only to perturb the electronic and steric properties of the metal centre.



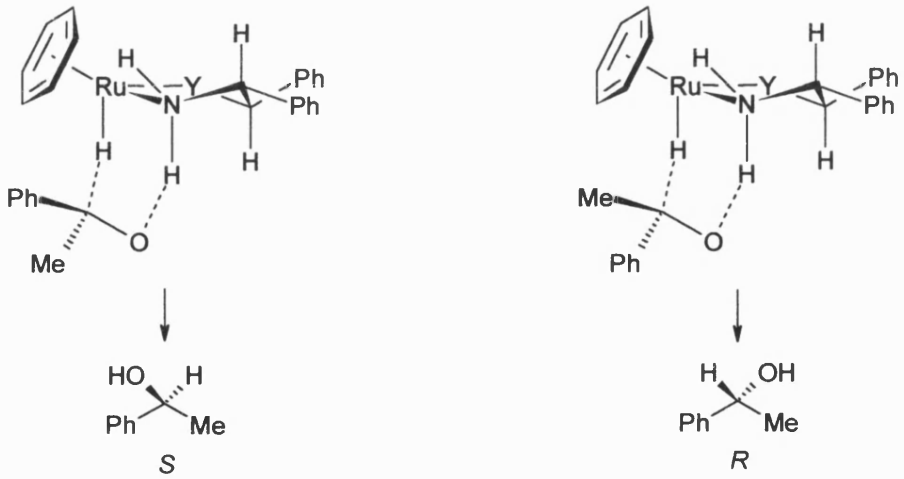
Scheme 76. Metal-ligand bifunctional catalysis.

2.3.1.2 Origin of Enantioselectivity

From the results given in Table 7 it clear that catalysts modified with 1*R*,2*R* configured aminosulfonamides (e.g. ligands **ent-56** & **65**) effect the reduction of acetophenone yielding an enantiomeric excess of (*R*)-1-phenylethanol. On the other hand, the catalyst containing ligand **56** having a 1*S*,2*S* configuration reduces acetophenone producing primarily (*S*)-1-phenylethanol. The sense of asymmetric induction observed is therefore in accordance with that reported by Noyori for catalysts incorporating monotosylated diamine ligands.[62] The exact origin of enantioselectivity in such systems has been discussed recently by Andersson,[67a] and of course, by Noyori.[67b] It seems reasonable to

extend the stereochemical arguments presented for Ru(II)-TsDPEN/β-amino alcohol systems to those involving polar aminosulfonamides **56**, **ent-56**, **65** and **66**.

Figure 21a schematically represents the diastereomeric transition states involved when diamine ligands with a 1*S*,2*S* configuration are employed in the catalytic system. It can be seen that this configuration forces a δ structure on the five-membered chelate ring, since the bulky phenyl substituents tend to occupy the 'equatorial' positions. Transfer hydrogenation via transition state **δ-85$_S$** affords (*S*)-1-phenylethanol, whilst the structure **δ-85$_R$** leads to (*R*)-1-phenylethanol. Differentiation between these diastereomeric transition states is a result of steric and electronic influences. Given the experimental results discussed above, it follows that structure **δ-85$_S$** represents the favoured transition state.



δ-85$_S$ - Favoured **δ-85$_R$** - Disfavoured

Figure 21a. Proposed diastereomeric transition states for systems involving (*S*,*S*)-TsDPEN (Y = NTs) *or* ligand **56** (Y = $NSO_2(p\text{-}C_6H_4SO_3Na)$).

For catalytic systems involving diamine ligands with a 1*R*,2*R* configuration, the five-membered chelate complex adopts a λ conformation. Transition states, which are mirror images of those in Figure 21a, may then be anticipated (Figure 21b). In this case, structure **λ-85$_R$** represents the favoured transition state, thus generating (*R*)-1-phenylethanol as the product.

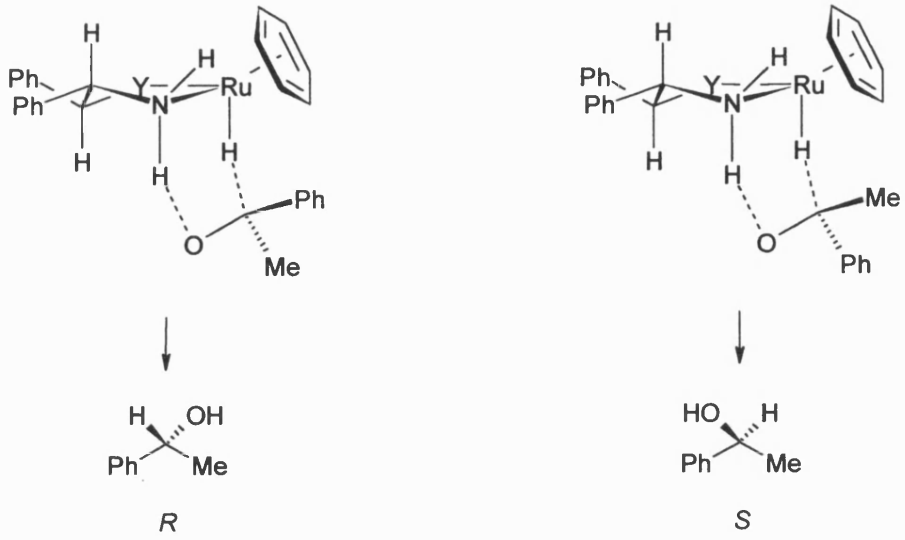
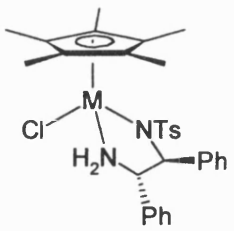


Figure 21b. Proposed diastereomeric transition states for systems involving (*R,R*)-TsDPEN (Y = NTs) *or* ligand **ent-56** (Y = $NSO_2(p\text{-}C_6H_4SO_3Na)$).

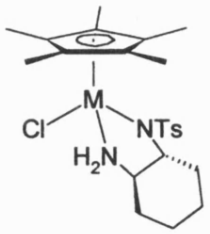
The preference for the more crowded transition states (e.g. **δ-85$_S$** & **λ-85$_R$**) is believed to be due to the operation of an attractive CH/π interaction[113] between the arene ligand of the complex and the aryl substituent in the ketone substrate.

2.3.2 Rhodium-Catalysed Asymmetric Transfer Hydrogenation

Rhodium(I) catalysts have generally performed poorly in asymmetric hydrogen transfer reactions. Complexes of enantiomerically pure phosphines,[93c] phenanthrolines,[114a] diamines,[114b,112] bipyridines[114c] and polyureas[114d,e] have been examined, and none of these have proved to be efficient catalysts. However, rhodium(III) complexes containing monotosylated diamine ligands are effective in the transfer reduction of aromatic ketones (Figure 22, M = Rh).[62b,c,e] Complexes **86** and **87** incorporate a pentamethylcyclopentadienyl ancillary ligand, and are therefore isoelectronic with the Ru(II) precatalyst **82** (Scheme 75). From the experimental data it is evident that Rh(III)-monotosylated diamine catalysts have the same mode of action as the corresponding Ru(II) complexes.



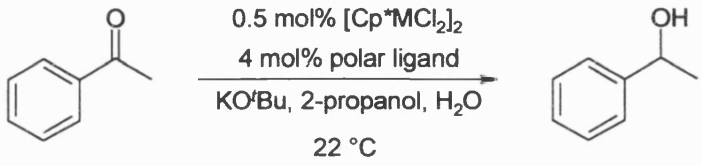
86



87

Figure 22. Rh(III) and Ir(III) complexes of monotosylated diamines (M = Rh, Ir).

The performance of polar aminosulfonamide ligands **56**, **ent-56**, **65** and **66** in the transfer reduction of various ketones was determined under the experimental conditions given in Scheme 77 (M = Rh). Thus, the enantiomerically pure rhodium complexes were prepared and used in an identical manner to that described for the analogous Ru(II)-aminosulfonamide complexes. Table 8 presents the results obtained.



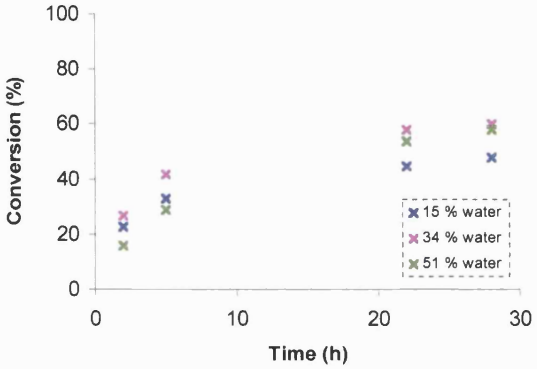
Scheme 77. Reaction conditions for Rh & Ir-catalysed asymmetric transfer reduction.

It is clear that the rate of reaction is strongly affected by the structure of the aminosulfonamide ligand. The rhodium complex incorporating diaminocyclohexane-based ligand **65** has a higher catalytic activity than the complexes containing diphenylethylenediamine-based ligands **56** and **66**. This finding is in agreement with that of Ikariya and co-workers, for the corresponding non-polar Rh(III) catalysts.[62e] Of the DPEN-based aminosulfonamides, it appears that ligand **66** is superior to ligand **ent-56** (or **56**). Also, a comparison of the results in Table 8 with those for the Ru(II) catalysts in Table 7, reveals that the rhodium-based catalysts generally have the higher activity and enantioselectivity. This order of reactivity is contrary to that exhibited by the analogous non-polar catalysts (see Table 1, page 27).

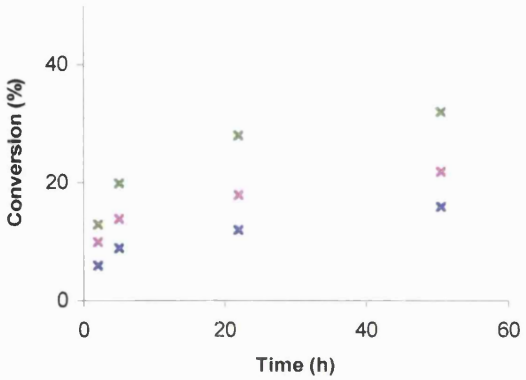
Ketone	Ligand	Reaction Time (h)	Conv. (%)	ee (%)	Configuration
81a	**ent-56**	22	45	97	*R*
81a	**65**	22	94	96	*R*
81a	**66**	45	68	96	*S*
81i	**56**	18	98	95	*S*
81i	**65**	4	99	94	*R*
81j	**ent-56**	26	93	97	*R*
81j	**65**	3	98	96	*R*
81j	**66**	19	97	97	*S*
81k	**56**	4	100	83	*S*
81k	**65**	2	100	88	*R*
81e	**56**	18	2	22	*S*
81e	**65**	18	40	76	*R*
81n	**56**	42	9	94	*S*
81n	**65**	42	65	95	*R*
81n	**66**	22	18	95	*S*
81o	**56**	64	81	82	*S*
81o	**65**	48	95	96	*R*
81b	**ent-56**	19	32	96	*R*
81b	**65**	19	93	95	*R*
81b	**66**	18	65	95	*S*

Table 8. Rh-catalysed asymmetric transfer hydrogenation of various aromatic ketones.

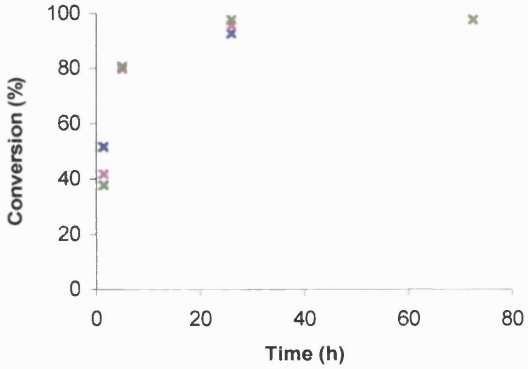
In order to determine the effect of an increase in water concentration, several rhodium-catalysed transfer hydrogenation experiments were carried out in a 2-propanol/water mixture containing 15, 34 and 51 % water. The results (Graphs 6 & 7) are somewhat surprising. It seems that the exact effect water has on the reaction depends upon the ligand and substrate involved in the system. For systems containing ligand **ent-56** and either acetophenone (Graph 6a) or *p*-methoxyacetophenone (Graph 6b), increasing the water concentration produced an increase in the reaction rate. This was most pronounced for the experiments involving electron rich, *p*-methoxyacetophenone. On



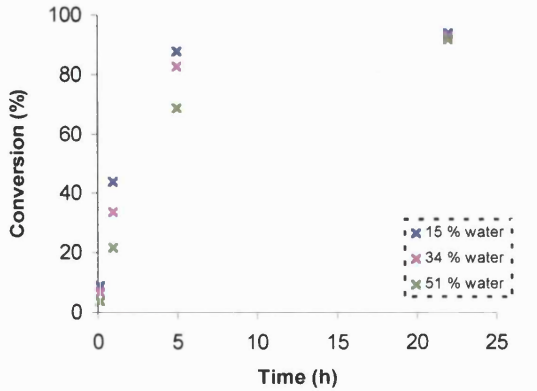
6a. Acetophenone/ligand **ent-56**.



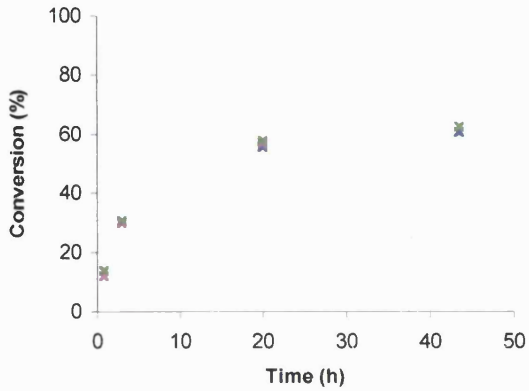
6b. *p*-Methoxyacetophenone/ligand **ent-56**.



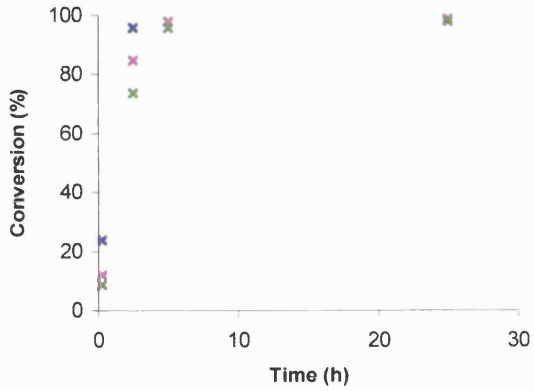
6c. *m*-Fluoroacetophenone/ligand **ent-56**.



6d. Acetophenone/ligand **65**.



6e. *p*-Methoxyacetophenone/ligand **65**.



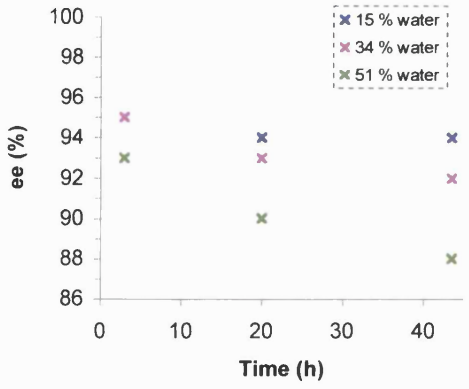
6f. *m*-Fluoroacetophenone/ligand **65**.

Graphs 6a → 6e. Variation in conversion with time and water concentration.

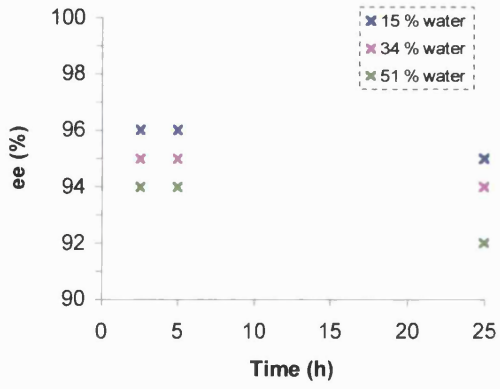
the other hand, the rate of reduction of electron poor *m*-fluoroacetophenone was reduced upon increasing the water concentration (Graph 6c). Also, it is apparent for each substrate, that the relative decrease in reaction rate with time is greatest in systems with a water concentration of 15 %.

For systems containing ligand **65** and either acetophenone (Graph 6d) or *m*-fluoroacetophenone (Graph 6f), the reaction rate is reduced upon increasing the water content. Using *p*-methoxyacetophenone as the substrate, the rate of reduction is very slightly increased at higher water concentrations (Graph 6e). The reason for these results is not clear; it was expected that an increase in water concentration (and therefore a decrease in the concentration of 2-propanol) would possibly have an adverse effect on the reaction rate.

It is evident from the data obtained that the resulting enantiomeric excess is also influenced by the concentration of water present in the reaction mixture. For systems involving ligand **65**, the initial enantiomeric excess observed decreases as the water content in the reaction mixture is increased. Also, erosion of the enantiomeric excess occurs more rapidly in experiments with high water concentrations (Graphs 7a & b). Experiments involving ligand **ent-56** however, displayed an enantiomeric excess that was stable over time and equal at the various water concentrations.



7a. *p*-Methoxyacetophenone/ligand **65**.



7b. *m*-Fluoroacetophenone/ligand **65**.

Graphs 7a & b. Variation of enantiomeric excess with time and water concentration.

2.3.3 Iridium-Catalysed Asymmetric Transfer Hydrogenation

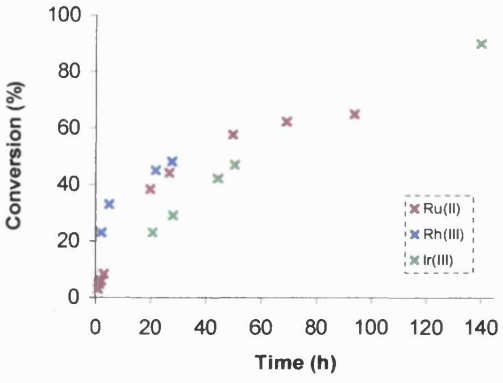
Like rhodium(I) complexes, iridium(I) complexes have lacked real success in the catalytic asymmetric transfer reduction of ketones. Amongst the most effective catalysts are those incorporating enantiomerically pure diamine ligands.[115c] Also, Pfaltz has communicated the use of bis-oxazoline ligands, which allowed ee's of up to 91 % to be attained.[115a] Other less successful Ir(I) complexes have utilised aminosulfide/aminosulfoxide,[115b] phosphine[115d,e] and pyridinimine ligands.[115f,g] Recently, the efficacy of monotosylated diamine ligands in Ir-catalysed hydrogen transfer reactions has been determined. Accordingly, the Ir(III) complexes shown in Figure 22 (M = Ir) proved reasonably effective, although somewhat less so than the analogous rhodium(III) catalysts.[62e]

The efficacy of aminosulfonamide ligands **ent-56** and **65** in iridium-catalysed hydrogen transfer was examined using the experimental conditions given in Scheme 77; the results are shown in Table 9. As expected, the catalytic system incorporating diaminocyclohexane-based ligand **65** is the most active. It is also apparent that the Ir-ligand **ent-56** catalyst complex is considerably less enantioselective than the Ir-ligand **65** complex. A difference in catalyst enantioselectivity is also evident for the Rh-catalysed systems, although it is not as marked.

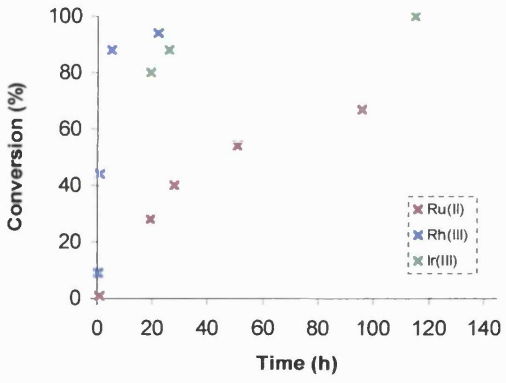
Comparison of the data in Tables 7, 8 & 9 allows some general conclusions to be made. Combination of rhodium or iridium with ligand **65** gives rise to superior catalysts in terms of activity and enantioselectivity. Of these, the rhodium-based catalyst is somewhat more active. The least effective metal-ligand combination is that of iridium and aminosulfonamide **ent-56**. Also, it appears that ligand **ent-56** is particularly unsuitable for use in the asymmetric reduction of substrates containing *ortho* substituents. Graphs 8 & 9 illustrate the comments above.

Ketone	Ligand	Reaction Time (h)	Conv. (%)	ee (%)	Configuration
81a	**ent-56**	140	90	82	*R*
81a	**65**	26	88	96	*R*
81f	**ent-56**	68	86	36	*R*
81f	**65**	21	99	73	*R*
81g	**ent-56**	163	89	24	*R*
81g	**65**	46	96	63	*R*
81h	**ent-56**	163	65	29	*R*
81h	**65**	92	95	66	*R*
81i	**ent-56**	43	95	86	*R*
81i	**65**	4	98	93	*R*
81j	**ent-56**	51	83	85	*R*
81j	**65**	26	99	94	*R*
81n	**ent-56**	150	22	78	*R*
81n	**65**	141	80	95	*R*
81m	**ent-56**	91	89	76	*R*
81m	**65**	25	98	94	*R*
81l	**ent-56**	91	93	76	*R*
81l	**65**	20	99	95	*R*
81o	**ent-56**	139	77	73	*R*
81o	**65**	45	96	96	*R*
81p	**ent-56**	139	41	91	*R*
81p	**65**	45	55	97	*R*

Table 9. Ir-catalysed asymmetric transfer hydrogenation of various aromatic ketones.

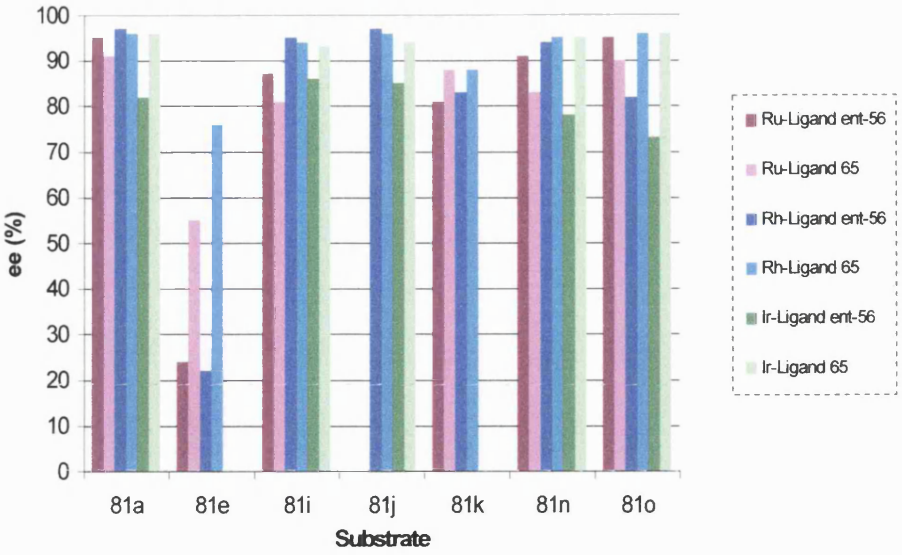


8a. Acetophenone/ligand **ent-56**.



8b. Acetophenone/ligand **65**.

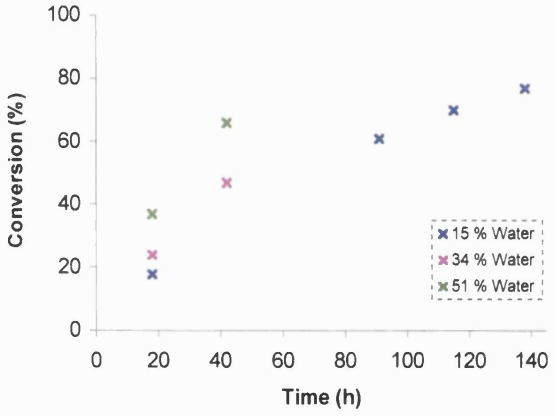
Graphs 8a & 8b. Comparison of activity.



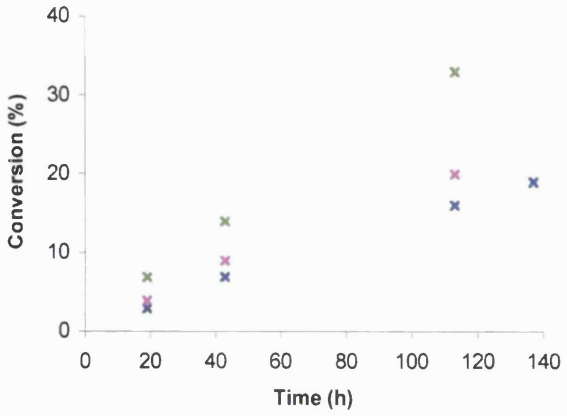
Graph 9. Comparison of enantiomeric excess.

Additional Ir-catalysed experiments were conducted with the reaction mixture containing higher concentrations of water; the results are shown on Graphs 10 & 11. It is evident that an increase in water content gives rise to a higher rate of reaction (Graphs 10a → 10e). For example, the initial rate of reduction of acetonaphthone (using ligand **ent-56**) in a reaction mixture containing 15 % water is almost doubled upon increasing the water content to 51 %. Unlike the rhodium-catalysed experiments, it seems that this effect is independent of the ligand and substrate involved in the system.

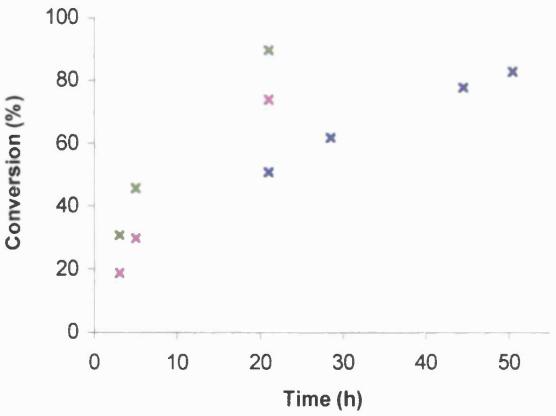
The enantiomeric excess is also affected by the water content in the reaction mixture. Systems involving ligand **65** behave in a manner similar to that of the corresponding rhodium systems. That is, the resulting enantiomeric excess is reduced as the water concentration is increased. Also, erosion of the enantiomeric excess occurs more rapidly in reactions with a high water content (Graphs 11a & b). Surprisingly, reactions involving ligand **ent-56** exhibit a marked *increase* in enantiomeric excess upon increasing the concentration of water in the reaction solvent. (Graphs 11c & d). In systems containing 51 % water, the reduction of acetonaphthone proceeds yielding a 93 % ee, whilst at the lower water concentration of 15 %, the enantiomeric excess obtained was just 74 %.



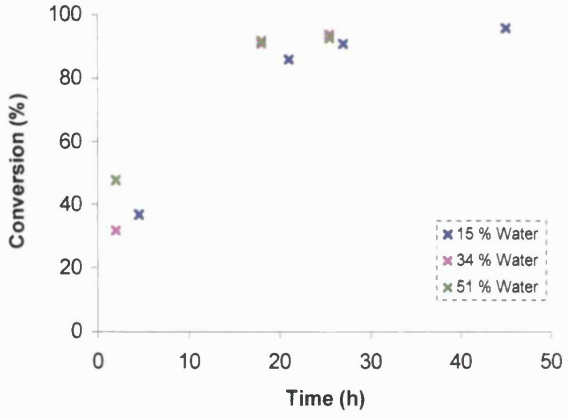
10a. 2-Acetonaphthone/ligand **ent-56**.



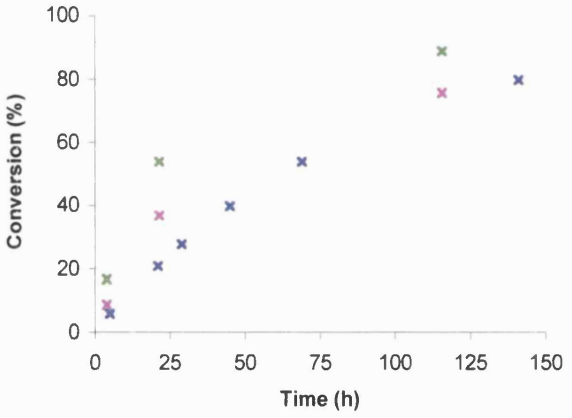
10b. *p*-Methoxyacetophenone/ligand **ent-56**.



10c. *m*-Fluoroacetophenone/ligand **ent-56**.

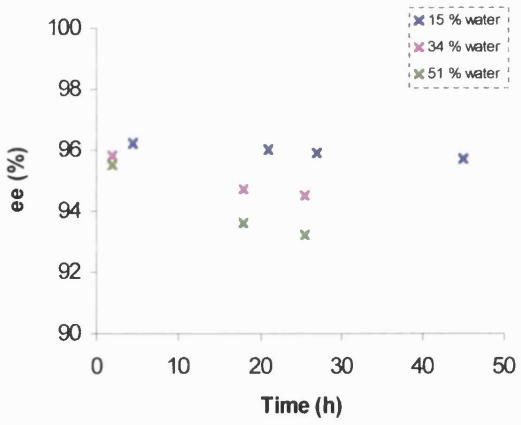


10d. 2-Acetonaphthone/ligand **65**.

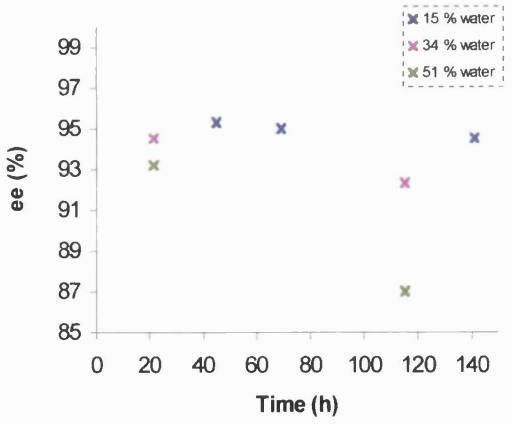


10e. *p*-Methoxyacetophenone/ligand **65**.

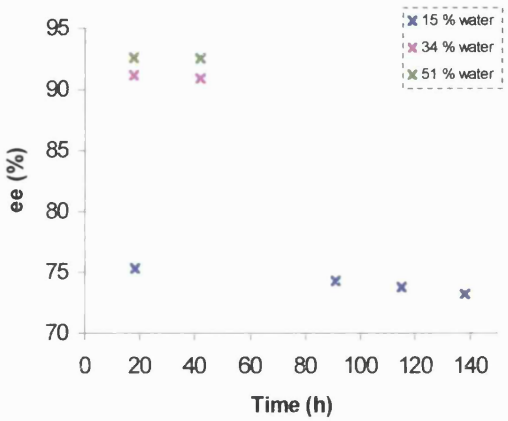
Graphs 10a → 10e. Variation in conversion with time and water concentration.



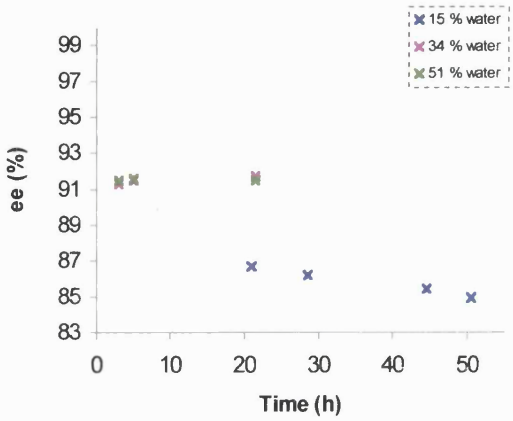
11a. Acetonaphthone/ligand **65**.



11b. *p*-Methoxyacetophenone/ligand **65**.



11c. Acetonaphthone/ligand **ent-56**.



11d. *m*-Fluoroacetophenone/ligand **ent-56**.

Graphs 11a → 11d. Variation of enantiomeric excess with time and water concentration.

There are many well-documented cases where the addition of water to the reaction mixture of organic and organometallic processes has led to beneficial effects, in terms of reaction rate and/or enantioselectivity.[1a,116] The role that water plays, is of course, dependant upon the reaction in question, and it is often a role which is poorly understood. For example, water may participate in the formation of secondary products which may then serve as catalysts or promoters. Or, the relative change in reaction rate/selectivity may be attributed to hydrogen bond interactions and hydrophobic effects. The latter explanation seems conceivable for asymmetric hydrogen transfer reactions. Hydrogen bonding to the carbonyl group of the ketone substrate would increase the bond polarisation. Consequently, the reduction process would be facilitated. Hydrophobic

effects may also be at work. These effects stem from the unique properties of water and play a crucial part in processes such as molecular recognition and the folding of biological macromolecules. Additional study is required in order to obtain a more exact explanation for the results obtained.

2.3.4 Summary

- Ruthenium, rhodium or iridium catalysts incorporating polar aminosulfonamide ligands **56**, **ent-56**, **65** and **66** proved effective in the asymmetric transfer reduction of various aromatic ketones under aqueous, homogeneous reaction conditions.
- The most effective catalytic system was obtained with rhodium as the central metal and ligand **65**. Enantioselective reduction of acetophenone to (*R*)-1-phenylethanol was then achieved with a conversion of 94 % and an enantiomeric excess of 96 %, in a reaction time of 22 hours.
- Variation of the water concentration in the reaction mixture affected both the rate and enantioselectivity of the reduction process in an unexpected manner. Notably, systems involving iridium and ligand **ent-56** were significantly enhanced upon increasing the concentration of water present.

2.3.5 Future Work

All of the transfer hydrogenation reactions described within this thesis have employed 2-propanol as a hydrogen donor with alkoxide as catalytic base. It would be more desirable to utilise formic acid as a hydrogen donor (as the azeotropic mixture with triethylamine) since this renders the reduction process irreversible. Given that Noyori has demonstrated the use of formic acid/triethylamine with Ru(II) catalysts containing TsDPEN,[62i] it should be possible to extend this methodology to systems incorporating polar aminosulfonamide ligands.

2.4 Development of Biphasic and Supported Aqueous Phase Systems for the Transfer Reduction of Aromatic Ketones

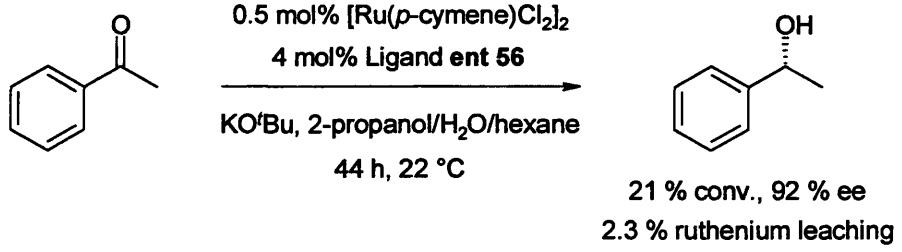
Having demonstrated the efficacy of polar aminosulfonamide ligands **56**, **ent-56**, **65** and **66** in enantioselective transfer hydrogenation under homogeneous conditions in aqueous media, the next stage of the project was to develop biphasic and SAP transfer reduction systems. If effective, such systems would allow the synthesis of enantiomerically enriched alcohols which would be free from transition metal residues. Additionally, catalyst recycling/recovery would be facilitated. The following sections describe the first steps towards realising biphasic and SAP catalytic asymmetric transfer hydrogenation. Unfortunately, research was hindered because transition metal leaching levels could not be measured easily. In fact, only ruthenium analysis was possible by means of inductively coupled plasma mass spectroscopy (ICP-MS).

2.4.1 Biphasic Asymmetric Transfer Hydrogenation

The construction of a biphasic transfer hydrogenation system is complicated by the use of 2-propanol as the hydrogen donor. On the one hand, its use may be advantageous since it can function as a co-solvent as well as a hydrogen donor, and therefore increase the solubility of the substrate in the aqueous layer. On the other hand, the use of 2-propanol may cause leaching of the catalyst into the organic phase, or in the worst case, may bring about homogenisation of the biphasic system. Whilst these considerations must be made, the reaction thermodynamics must also be taken into account. Unfortunately, the use of a large excess of 2-propanol is required in order to drive the reaction equilibrium to favour the products.[55] Thus, the concentration of 2-propanol in the biphasic system should prove very important and will need to be optimised in order to achieve respectable yields and low levels of transition metal leaching.

Due to its extremely low polarity, hexane was the bulk organic solvent chosen for use in the biphasic system. Consequently, the likelihood of forming a homogeneous system upon the addition of the other reaction components is minimal. Polar catalyst complexes were prepared *in situ* using an identical procedure to that described in Section 2.3.1. Then, water and a solution of KO^{t}Bu in 2-propanol was added along with the ketonic substrate dissolved in hexane (2-propanol/ H_2O/Hexane = 1 : 2.1 : 2.5), thus providing a two-phase system. Following vigorous mixing at room temperature, the phases were allowed to separate and the upper organic phase analysed.

Using acetophenone as the substrate, the biphasic reaction proceeded with a 21 % conversion after 44 hours. 1-Phenylethanol was obtained with an enantiomeric excess of 92 %. Ruthenium analysis indicated that 2.3 % of the ruthenium contained within the catalyst had leached into the organic phase during reaction (Scheme 78). Further results are presented in Table 10.



Scheme 78. Asymmetric transfer reduction under biphasic conditions.

Ruthenium-Catalysed Asymmetric Transfer Hydrogenation

As expected, the results for the reactions under biphasic conditions were not as good as those for the corresponding reactions under homogeneous conditions. Significant decreases in rate and enantioselectivity were observed. Lower relative reaction rates are the likely result of poor substrate solubility in the aqueous phase, whilst the lower enantioselectivity stems from the differing solvent environment and/or presence of an interface. Also, the concentration of 2-propanol in the biphasic system is less than that

in the homogeneous system, and it is distributed between the organic and aqueous phases. This causes the position of equilibrium to shift to the left, thus reducing the maximum conversion obtainable. Two phase reactions carried out at 30 °C proceeded with a higher rate but lower enantioselectivity.

Ruthenium leaching levels for each reaction are comparable, although it can be observed that systems which incorporate ligand **65** have slightly lower leaching levels than those containing ligand **ent-56**. This is not surprising, since the higher polarity of the ruthenium-ligand **65** complexes make them less soluble in the bulk organic solvent.

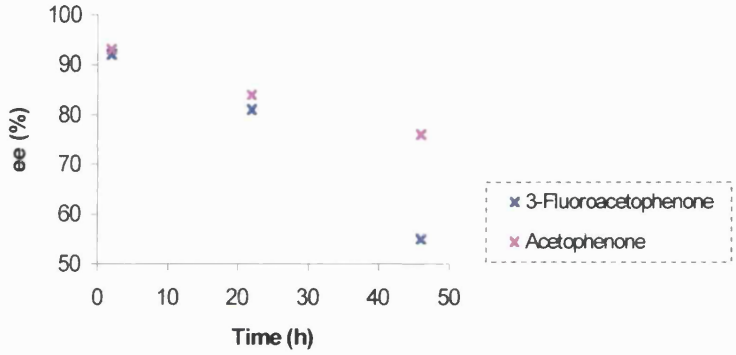
Ketone	Ligand	Metal	Reaction Time (h)	Conv. (%)	ee (%)	Leaching (mg, %)
81a	**ent-56**	Ru	44	21	92	0.046, 2.3
81i	**ent-56**	Ru	44	26	80	0.050, 2.5
81a	**65**	Ru	44	20	86	0.030, 1.5
81i	**65**	Ru	44	26	80	0.045, 2.2
81a*	**65**	Ru	19	30	83	-
81i*	**65**	Ru	19	38	78	-
81a	**65**	Ir	22	73	84	-
81i	**65**	Ir	22	95	90	-
81j	**65**	Ir	22	91	81	-
81m	**65**	Ir	22	85	88	-

Table 10. Asymmetric transfer reduction under biphasic conditions (* Reaction temp. 30 °C).

Iridium-Catalysed Asymmetric Transfer Hydrogenation

Results from the iridium-catalysed experiments were much more encouraging, with reasonable conversions and ee's being obtained in relatively short reaction times. Once again, decreases in reaction rate and enantioselectivity were observed relative to the corresponding homogeneous systems, although this was not as marked as for the ruthenium-catalysed reactions. It was shown in Section 2.3.3 that increasing the

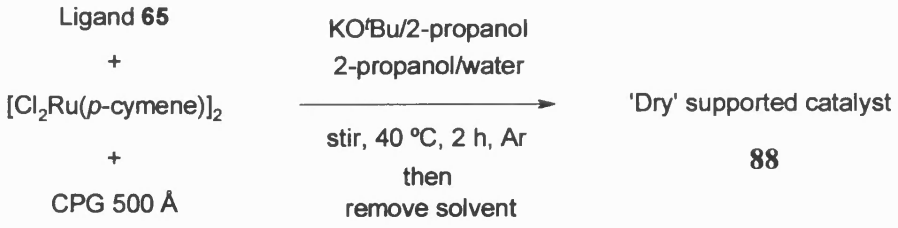
concentration of water in iridium-catalysed reactions had a beneficial effect on the rate of reduction. Therefore, in biphasic reactions, there are two conflicting influences on reaction rate. Whilst the high water content (34 %) promotes the reduction process, the substrate insolubility in the aqueous phase, impedes the reaction. Also notable in the biphasic systems was the extremely rapid erosion of enantiomeric excess (Graph 12). At a reaction time of 2 hours, the enantiomeric excess observed in the reaction system containing 3-fluoroacetophenone was 92 %. However, after 46 hours this had decreased to just 55 %. Homogeneous systems having a high water content also displayed this trait.



Graph 12. Variation of enantiomeric excess with time.

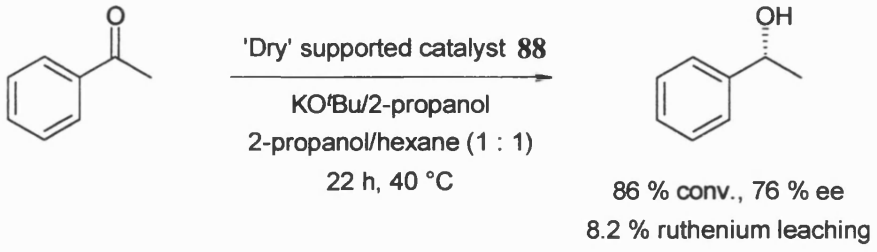
2.4.2 SAP Asymmetric Transfer Hydrogenation

It was envisaged that 2-propanol as a hydrogen donor, would be incompatible with the supported aqueous phase catalyst since it would dissolve the aqueous film from the CPG support. As a result, the catalytic activity and selectivity may be reduced. Nevertheless, the efficacy of a SAP catalyst in the presence of 2-propanol, needed to be determined. Therefore, a supported catalyst was prepared as shown in Scheme 79.[91a] The catalyst precursor $[RuCl_2(p\text{-cymene})]_2$ was added to a deoxygenated aqueous solution of ligand **65**, which also contained CPG 500 Å. Stirring the mixture at 40 °C for two hours ensured complexation and that the CPG had an even coating of the ruthenium catalyst. Removal of the solvent afforded the 'dry' supported catalyst **88**.



Scheme 79. Procedure for the preparation of a SAP catalyst.

In order to gauge the performance of a SAP catalyst with a very low water content, acetophenone was treated with the prepared ruthenium catalyst **88** (1 mol% based on ruthenium) in the presence of base and 2-propanol, in a bulk solvent of hexane (Scheme 80). At the end of the reaction, the solution was decanted and analysed. Surprisingly, the percent conversion achieved after a reaction time of 22 hours is comparable to that of the corresponding homogeneous reaction. This result would be expected if the majority of the catalyst had leached into solution during reaction. However, the level of ruthenium found in the bulk solvent indicates that more than 90 % of the ruthenium present in the system remained on the CPG support at the end of the reaction. The enantiomeric excess achieved using the 'dry' supported catalyst is somewhat lower than that obtained in the analogous reaction under homogeneous conditions. Without knowing the exact water content of catalyst and with only this result, it is difficult to comment upon the relationship between catalyst activity/selectivity and water content. Further experimentation is required.



Scheme 80. Asymmetric transfer reduction of acetophenone using a 'dry' SAP catalyst.

2.4.3 Catalyst Removal by Aqueous Extraction

Upon completion of homogeneous transfer hydrogenation reactions, aqueous extraction can be used to separate the catalyst (containing the polar aminosulfonamide ligand) from the product. All volatiles (i.e. remaining 2-propanol and acetone) were first removed from the reaction mixture under reduced pressure, and then water and hexane added in order to provide a two-phase system. Following vigorous mixing at room temperature, the phases were allowed to separate. The upper organic phase containing the reaction products was then isolated and analysed. Table 11 shows the results obtained after performing only one aqueous extraction. Hence, this is an effective technique for catalyst removal from homogeneous reaction mixtures.

Ketone	Ligand	Metal	Reaction Time (h)	Conv. (%)	ee (%)	Leaching (mg, %)
81i	**ent-56**	Ru	19	69	88	0.009, 0.45
81i	**65**	Ru	19	81	80	0.007, 0.35

Table 11. Product assay after performing an aqueous extraction.

2.4.4 Summary

- The application of enantiomerically pure aminosulfonamide ligands in aqueous biphasic transfer hydrogenation reactions has been demonstrated.
- The preparation of a SAPC for asymmetric transfer hydrogenation has been achieved. However, it has yet to be effectively applied.
- Upon completion of a homogeneous transfer hydrogenation reaction, the catalyst can be effectively separated from the product by means of aqueous extraction.

The work described in this section is just a fraction of the research which is needed to realise effective biphasic and SAP catalytic asymmetric transfer hydrogenation systems. Unfortunately, only reactions employing ruthenium catalysts could be analysed

completely since an ICP-MS facility was not available for the measurement of rhodium or iridium levels. Under homogeneous conditions, ruthenium catalysts were not the most effective and therefore the few results described above may not reflect the true potential of biphasic and SAP techniques.

2.4.5 Future Work

Future research should initially utilise rhodium-based catalysts since they provide the highest activity. The use of 2-propanol as a hydrogen donor is likely to cause difficulties, and therefore other sources of hydrogen should be investigated. A very recent publication describes the use of sodium formate as a hydrogen donor for asymmetric transfer reductions in aqueous media.[117] Sodium formate constitutes an ideal hydrogen source for biphasic hydrogen transfer reactions for several reasons. First of all, the dehydrogenated product of sodium formate is gaseous carbon dioxide, and since this is free to leave the reaction mixture the transfer hydrogenation process is rendered irreversible. Additionally, carbon dioxide will not contaminate the aqueous layer in which the catalyst is contained. Therefore, the catalyst recycling process is facilitated. Finally, sodium formate should not cause leaching of the organometallic catalyst complex into the bulk organic solvent.

A successful SAP catalyst will surely utilise a formic acid-based hydrogen donor. As mentioned previously, the formic acid/triethylamine azeotropic mixture has proved most useful in standard homogeneous reactions. The advantages of a SAP system would be enhanced if the triethylamine (or other tertiary amine base) could be employed catalytically, since the base could then reside in the aqueous film upon the support surface, and therefore would not contaminate the final product. Formic acid would then be added slowly, as required. At the end of the reaction the organic solvent would contain only residual formic acid and the reaction product.

Chapter 3

Experimental

3.1 General Procedures

Commercially available solvents and reagents were obtained from Sigma-Aldrich Company Ltd, Lancaster Synthesis Ltd and Fisher Scientific Ltd and were used throughout without further purification, apart from the following. Dichloromethane was distilled from calcium hydride and triethylamine was distilled from, and stored over potassium hydroxide. Solvents and reagents were deoxygenated where necessary by purging with argon. 'Petrol' refers to the fraction of petroleum ether boiling in the range of 40 – 60 °C.

Analytical thin layer chromatography was performed on pre-coated glass-backed silica gel (Merck Kieselgel 60 F_{254}) plates and visualised under ultra-violet light (at 254 nm) or by staining with potassium permanganate, vanillin or ninhydrin solution. Column chromatography was carried out using Merck Kieselgel 60 H silica gel.

Melting points were measured on a Büchi 535 instrument. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter. Infrared spectra were measured in the range of 4000 – 600 cm^{-1} using a Perkin-Elmer 1600 series FT-IR spectrophotometer, with internal calibration. Spectra were recorded as potassium bromide disks or as thin films. Elemental analyses were performed using a Carlo Erba 1106 Elemental Analyser or an Exeter Analytical Inc CE-440 Elemental Analyser. Fast atom bombardment (FAB) and electrospray (ES) mass spectra were obtained using a Fisons VG Autospec.

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on either a Jeol EX-400, a Bruker 300 or on a Jeol GX-270 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm), and are relative to an internal reference of residual protic solvent. The

multiplicities of the spectroscopic data are presented in the following manner: singlet (s), apparent singlet (app. s), broad singlet (br s), doublet (d), doublet of doublets (dd), double doublet of doublets (ddd), triplet (t), apparent triplet (app. t), apparent triplet of doublets (app. td) and multiplet (m). Coupling constants (*J*) are expressed in Hz. The assignment of aromatic proton resonances for *para* disubstituted benzene rings has been simplified by assuming an AB system, however, the characteristic features of an AA'BB' system were observed in the NMR spectra.

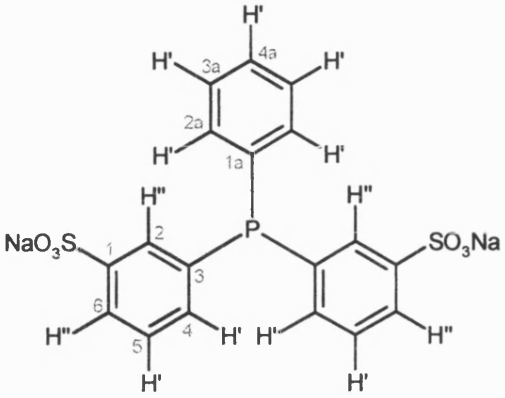
Gas chromatographic analysis was performed on a Fisons GC 8000 series instrument using a Supelco β-Dex 120 fused silica capillary column with a 60 m length, 0.25 mm internal diameter and 0.25 μm film thickness. Error in measurement: ± 0.5 %.

Ruthenium analysis was carried out using inductively coupled plasma mass spectrometry (ICP-MS) by Morgan Materials Technology Ltd. Palladium analysis was performed using atomic absorption (AA) on a Varian AA-275 series spectrometer. A hollow cathode lamp provided the light source, and was purchased from S+S Juniper Ltd. A palladium atomic absorption standard solution (1000 $\mu g/cm^3$ in 5 wt% hydrochloric acid) was purchased from Sigma-Aldrich Company Ltd and diluted as necessary to provide a range of calibration standards.

Single crystal X-ray diffraction data was collected on a Nonius Kappa CCD machine. Structure determination and refinement were achieved using the SHELX suite of programmes; drawings were produced using ORTEX.

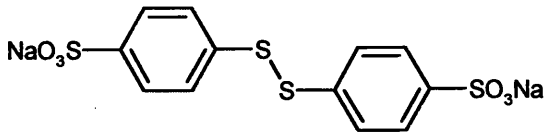
3.2 Experimental Procedures for Ligand Syntheses

Disodium 3-[phenyl(3-sulfonatophenyl)phosphino]benzenesulfonate (TPPDS-Na)



Triphenylphosphine (3.0 g, 11.4 mmol) and concentrated sulfuric acid (21 cm^3) were stirred at room temperature until dissolution. The solution was then cooled to 0 °C before the slow addition of oleum (9.5 cm^3, 65 wt% SO_3). After stirring at room temperature for 21 hours, the reaction mixture was neutralised at 0 °C by the slow, dropwise addition of sodium hydroxide solution (157 cm^3, 7.5 M). Removal of water under reduced pressure produced a colourless residue which was heated at reflux in methanol (300 cm^3) for 30 minutes, and then filtered hot to remove sodium sulfate. The filtrate was reduced to dryness and the residue redissolved in hot methanol (300 cm^3). The addition of ethyl acetate (850 cm^3) caused the precipitation of disodium 3-[phenyl(3-sulfonatophenyl)phosphino]benzenesulfonate (3.45 g, 7.4 mmol, 65 %) as a fine colourless powder, δ_H(270 MHz; D_2O) 7.82 – 7.68 (4H, m, H'') and 7.40 – 7.16 (9H, m, H'); δ_C(67.8 MHz; D_2O) 142.8 (s, C-1), 136.9 (d, $^1J_{(PC)}$ 11.0, C-3), 135.9 (d, $^2J_{(PC)}$ 17.6, C-2), 134.3 (d, $^1J_{(PC)}$ 4.4, C-1a), 133.5 (d, $^2J_{(PC)}$ 19.9, C-2a), 129.8 (d, $^2J_{(PC)}$ 23.2, C-4), 129.6 (s, C-4a), 129.2 (d, $^3J_{(PC)}$ 5.5, C-5), 128.8 (d, $^3J_{(PC)}$ 7.8, C-3a) and 126.1 (s, C-6); $\delta_{P\{H\}}$(121.5 MHz; D_2O) –5.08; *m/z* (FAB-) 442.9785 (100 %, $[M\text{-}Na^+]^-$ – $C_{18}H_{13}NaO_6PS_2$ requires 442.9789), 264 (43) and 111 (49).

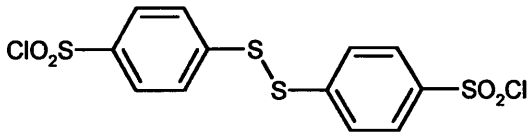
Disodium 4-[(4-sulfonatophenyl)disulfanyl]benzenesulfonate (67)[96]



Sulfanilic acid (47.5 g, 0.27 mol) and anhydrous sodium carbonate (13.3 g, 0.13 mol) were dissolved in water (500 cm^3) by warming. The solution was cooled to 15 °C and sodium nitrite (18.5 g, 0.27 mol) in water (50 cm^3) was added. The mixture was poured slowly into concentrated hydrochloric acid (52.5 cm^3, 0.64 mol) and crushed ice (300 g), and the resulting suspension of 4-diazoniobenzenesulfonate stirred for 15 minutes.

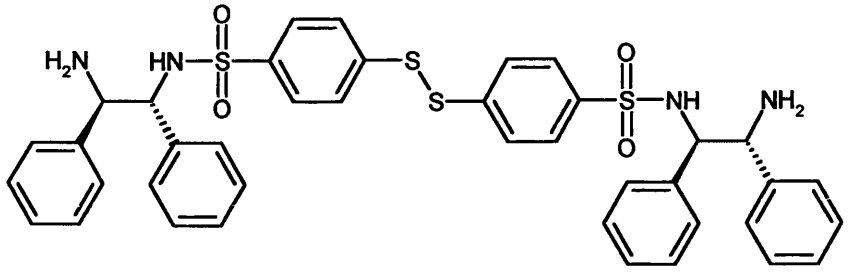
Sodium sulfide nonahydrate (65.0 g, 0.27 mol) and powdered sulfur (8.5 g, 0.27 mol) were dissolved in water (75 cm^3) at 100 °C. A solution of sodium hydroxide (10.0 g, 0.25 mol) in water (100 cm^3) was added, and the resulting disodium disulfide solution cooled to 0 °C. The suspension of 4-diazoniobenzenesulfonate was then added over a period of 1 hour, along with ice (50 – 100 g), so as the temperature of the reaction mixture remained below 5 °C. After stirring the solution at room temperature until the evolution of nitrogen had ceased (20 hours), the reaction mixture was acidified to pH 2 using concentrated hydrochloric acid. The precipitated sulfur was removed by vacuum filtration, and the solution concentrated to a volume of 400 cm^3 by evaporating the water at 100 °C and atmospheric pressure. After adjustment of pH to pH 7 with a concentrated solution of sodium hydroxide, the reaction mixture was allowed to stand overnight at room temperature. During this time crystallisation produced light brown plates (37.8 g, 89.5 mmol, 66 %), which were collected by filtration and dried under high vacuum. δ_H(270 MHz; D_2O) 7.71 (4H, d, *J* 8.4, Ar-*H*) and 7.61 (4H, d, *J* 8.4, Ar-*H*); δ_C(100.5 MHz; D_2O) 144.0 (C), 142.7 (C), 129.7 (CH) and 129.1 (CH); *m/z* (ES-) 399 (100 %, M - Na), 377 (51) and 220 (96).

4-{[4-(chlorosulfonyl)phenyl]disulfanyl}benzenesulfonyl chloride (68)



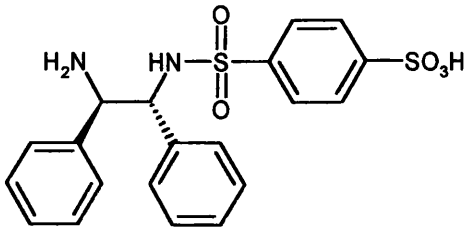
A mixture of disodium 4-[(4-sulfonatophenyl)disulfanyl]benzenesulfonate **67** (10.0 g, 23.7 mmol), phosphorus pentachloride (5.0 g, 24 mmol) and phosphorus oxychloride (10.0 cm^3, 107 mmol) were heated at reflux (120 °C) for 2 hours. After cooling to room temperature, dichloromethane (50 cm^3) was added and the resulting mixture poured onto ice. Following 1 hour of intensive stirring, the organic layer was separated and stirred with concentrated sodium hydrogencarbonate solution (100 cm^3) for a further hour. The organic layer was once again separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure to a volume of approximately 25 cm^3. The slow addition of cyclohexane caused the precipitation of sulfonyl chloride **68** (6.4 g, 15.4 mmol, 65 %) which was isolated by filtration as a light brown powder, mp 135 °C (lit.,[98] 142 °C); (Found: C, 34.7; H, 1.97. $C_{12}H_8Cl_2O_4S_4$ requires C, 34.7; H, 1.94); ν_{max}(KBr disc)/cm^{-1} 3071 (aryl–H), 1570 (C=C) and 1372 (SO_2–Cl); δ_H(270 MHz; $CDCl_3$) 8.00 (4H, d, *J* 8.9, Ar-*H*) and 7.69 (4H, d, *J* 8.9, Ar-*H*); δ_C(100.5 MHz; $CDCl_3$) 145.0 (C), 143.0 (C), 128.1 (CH) and 126.7 (CH); *m/z* (FAB+) 413.8686 (35 %, M^+ – $C_{12}H_8Cl_2O_4S_4$ requires 413.8683), 133 (55), 111 (63) and 97 (100).

N-[(1R,2R)-2-amino-1,2-diphenylethyl]-4-{[4-({[(1R,2R)-2-amino-1,2-diphenyl ethyl]amino}sulfonyl)phenyl]disulfanyl}benzenesulfonamide (ent-69)



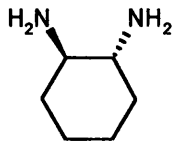
A solution of 4-{[4-(chlorosulfonyl)phenyl]disulfanyl}benzenesulfonyl chloride **68** (3.32 g, 8.0 mmol) in dichloromethane (10 cm^3) was added dropwise to a mixture of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (3.73 g, 17.6 mmol) and triethylamine (5.0 cm^3, 3.6 g, 36 mmol) in dichloromethane (50 cm^3) at 0 °C. The reaction mixture was stirred for 2 hours at room temperature, and then concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2, CH_2Cl_2 followed by CH_2Cl_2/MeOH – 25:1, detection – UV and ninhydrin). *Sulfonamide* **ent-69** (5.46 g, 7.1 mmol, 89 %) was obtained as a pale yellow powder, mp 103 – 105 °C; $[\alpha]_D^{22}$ +100 (*c* 1.35, CH_3OH); ν_{max}(KBr disc)/cm^{-1} 3278 (SO_2N–H), 3061 (aryl–H), 1578 (H–N–H), 1494 (C=C), 1328 (O=S=O) and 1164 (SO_2–N); δ_H(270 MHz; $CDCl_3$) 7.34 (4H, d, *J* 8.6, Ar-*H*), 7.20 (4H, d, *J* 8.6, Ar-*H*), 7.12 (20H, app. d, Ph), 4.42 (2H, d, *J* 5.1, CH_AH$_B$C) and 4.18 (2H, d, *J* 5.1, CH$_A$$H_B$C); δ_C(67.5 MHz; CD_3OD) 142.3 (C), 142.2 (C), 141.5 (C), 139.9 (C), 129.4 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 127.4 (CH), 66.9 (CH) and 62.4 (CH); *m/z* (ES+) 767.1839 (10 %, $[MH]^+$ – $C_{40}H_{39}N_4O_4S_4$ requires 767.1854), 367 (63) and 195 (100).

4-({[(1*R*,2*R*)-2-amino-1,2-diphenylethyl]amino}sulfonyl)benzenesulfonic acid (ent-56)



Sodium hydroxide (10 cm^3 of a 2.5 M solution in water, 25 mmol) and hydrogen peroxide (5 cm^3 of a 27.5 wt % solution in water) were added to a solution of sulfonamide **ent-69** (4.76 g, 6.21 mmol) in methanol (50 cm^3). The resulting mixture was stirred for 2 hours, before the addition of a further 2 cm^3 of hydrogen peroxide solution. After 12 hours stirring at room temperature, concentrated sodium hydrogen sulfite solution (10 cm^3) was added, and the mixture allowed to stir for an additional 2 hours. The solution pH was then measured and adjusted to approximately pH 6 using 1 M sodium hydroxide solution. The reaction mixture was concentrated to dryness under reduced pressure, water (50 cm^3) added and then stirred for 30 minutes. After vacuum filtration and washing with water (100 cm^3), ethanol (50 cm^3) and dichloromethane (50 cm^3), *sulfonic acid* **ent-56** (4.23 g, 9.8 mmol, 78 %) was isolated as a colourless powder, mp > 280 °C (decomposition); $[\alpha]_D^{22}$ +70 (*c* 1.66 in $(CH_3)_2SO$); ν_{max}(KBr disc)/cm^{-1} 3041 (NH_3^+), 1621 (NH_3^+), 1529 (C=C), 1327 (O=S=O) and 1163 (SO_2–N); δ_H(400 MHz; $(CD_3)_2SO$) 8.39 (4H, br s, NH), 7.43 (2H, d, *J* 8.6, Ar-*H*), 7.38 (2H, d, *J* 8.6, Ar-*H*), 7.17 (5H, app. s, Ph), 6.94 – 6.76 (5H, m, Ph), 4.62 (1H, d, *J* 10.2, CH_AH_BC) and 4.38 (1H, d, *J* 10.2, CH_AH_BC); δ_C(75.5 MHz; $(CD_3)_2SO$) 151.6 (C), 141.5 (C), 136.1 (C), 134.8 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.92 (CH), 127.87 (CH), 126.4 (CH), 126.0 (CH), 61.9 (CH) and 58.9 (CH); *m/z* (ES-) 431.0760 (100 %, $[M\text{-}H^+]^-$ – $C_{20}H_{19}N_2O_5S_2$ requires 431.0735), 325 (36) and 219 (13).

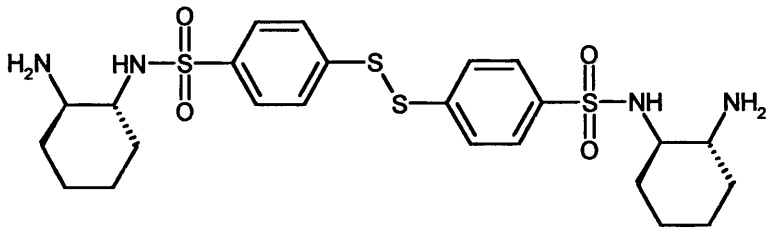
(1*R*,2*R*)-(-)-1,2-diaminocyclohexane[102]



(1*R*,2*R*)-(-)-1,2-diaminocyclohexane was obtained by the resolution of *trans*-1,2-diaminocyclohexane. A beaker equipped with an overhead stirrer was charged with (2*R*,3*R*)-(+)-tartaric acid (150 g, 0.99 mol) and water (400 cm^3). The mixture was stirred at room temperature until complete dissolution occurred, at which point *trans*-1,2-diaminocyclohexane (240 cm^3, 228 g, 2.0 mol) was added at a rate such that the reaction temperature just reached 70 °C. To the resulting solution, glacial acetic acid (100 cm^3, 1.75 mol) was added at a rate such that the reaction temperature just reached 90 °C. The reaction mixture was stirred vigorously as it cooled to room temperature over a 2 hour period. The slurry was then cooled to approximately 5 °C for a further 2 hours, and the precipitate collected by vacuum filtration. The wet cake was washed with ice cold water (100 cm^3) followed by methanol (5 x 100 cm^3) and dried at 40 °C under reduced pressure. (1*R*,2*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate salt (256 g, 0.97 mmol, 97 %) was obtained as a pale pink solid, $[\alpha]_D^{22}$ +13 (*c* 4 in H_2O).

Potassium hydroxide solution (114 cm^3 of a 7 M solution in water, 0.8 mol) was added directly to (1*R*,2*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate (100 g, 0.38 mol). The upper layer containing the diamine was removed immediately, and stored over potassium hydroxide pellets before distilling from potassium hydroxide under reduced pressure. (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (24 g, 0.21 mol, 55 %) crystallised on standing, mp 42 – 44 °C; bp 88 – 95 °C at 20 mmHg; $[\alpha]_D^{22}$ -24 (*c* 5 in 1 M HCl).

N-[(1R,2R)-2-aminocyclohexyl]-4-{[4-({[(1R,2R)-2-aminocyclohexyl]amino} sulfonyl)phenyl]disulfanyl}benzenesulfonamide (70)



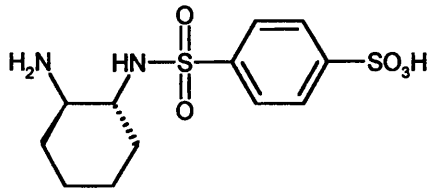
Method A

A solution of 4-{[4-(chlorosulfonyl)phenyl]disulfanyl}benzenesulfonyl chloride **68** (2.91 g, 7.0 mmol) in dichloromethane (10 cm^3) was added dropwise to a mixture of (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (1.76 g, 15.4 mmol) and triethylamine (5 cm^3, 3.6 g, 36 mmol) in dichloromethane (50 cm^3) at -78 °C. The reaction mixture was allowed to reach room temperature, and then stirred for 2 hours before concentrating under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2 followed by CH_2Cl_2/MeOH – 5:1, detection – UV and ninhydrin). *Sulfonamide* **70** (3.44 g, 6.0 mmol, 86 %) was obtained as a pale yellow powder, mp 125 – 128 °C; $[\alpha]_D^{22}$ +36.5 (*c* 2, CH_3CH_2OH); ν_{max}(KBr disc)/cm^{-1} 3348 & 3265 (N–H), 3071 (aryl–H), 2933 & 2849 (H–C–H), 1581 (C=C), 1324 (O=S=O) and 1162 (SO_2–N); δ_H(400 MHz; CD_3OD) 7.84 (4H, d, *J* 8.8, Ar-*H*), 7.68 (4H, d, *J* 8.8, Ar-*H*), 2.78 (2H, ddd (app. td), *J* 10.4, and 4.3, CH_AH$_B$C), 2.42 (2H, ddd (app. td), *J* 10.4, and 4.0, CH$_A$$H_B$C), 1.98 – 1.86 (2H, m, Cy), 1.69 – 1.48 (4H, m, Cy) and 1.39 – 1.00 (10H, m, Cy); δ_C(100.5 MHz; CD_3OD) 142.6 (C), 141.9 (C), 128.7 (CH), 127.8 (CH), 60.3 (CH), 55.8 (CH), 33.8 (CH_2), 33.0 (CH_2), 26.1 (CH_2) and 25.5 (CH_2); *m/z* (FAB+) 571.1551 (100 %, $[MH]^+$ – $C_{24}H_{35}N_4O_4S_4$ requires 571.1541), 286 (20) and 96 (33).

Method B

A solution of 4-{[4-(chlorosulfonyl)phenyl]disulfanyl}benzenesulfonyl chloride **68** (23.3 g, 56.1 mmol) in dichloromethane (80 cm^3) was added dropwise to a mixture of (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (14.08 g, 0.123 mol) and triethylamine (40 cm^3, 29 g, 0.29 mol) in dichloromethane (400 cm^3) at -78 °C. The reaction mixture was allowed to reach room temperature, and then stirred for 2 hours before removing all solvent and volatiles under reduced pressure. The solid residue was dissolved in dichloromethane (200 cm^3) and extracted initially with water (200 cm^3) and then concentrated sodium hydrogencarbonate solution (40 cm^3). After drying the organic layer over sodium sulfate, the solvent was removed under reduced pressure yielding *sulfonamide* **70** (25.9 g, 45.4 mmol, 81 %) as a slightly yellow powder, mp 108 – 110 °C; δ_H(400 MHz; $CDCl_3$) 7.75 (4H, d, *J* 8.8, Ar-*H*), 7.60 (4H, d, *J* 8.8, Ar-*H*), 2.69 – 2.58 (2H, m, CH_AH_BC), 2.29 – 2.18 (2H, m, CH_AH_BC), 1.85 – 1.74 (2H, m, Cy), 1.61 – 1.38 (4H, m, Cy), 1.30 – 1.19 (2H, m, Cy) and 1.14 – 0.90 (8H, m, Cy); *m/z* (FAB+) 571 (100 %, $[MH]^+$).

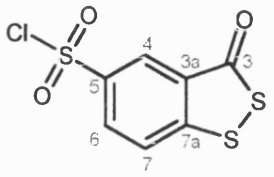
4-({[(1*R*,2*R*)-2-aminocyclohexyl]amino}sulfonyl)benzenesulfonic acid (65)



Sodium hydroxide (88.0 cm^3 of a 1 M solution in water, 88.0 mmol) and hydrogen peroxide (34 cm^3 of a 35 wt % solution in water) were added to a solution of sulfonamide **70** (25.0 g, 43.8 mmol) in methanol (440 cm^3). The resulting mixture was stirred for 2 hours, before the addition of a further 15 cm^3 of hydrogen peroxide solution. After 12 hours stirring at room temperature, concentrated sodium hydrogen sulfite solution (80 cm^3) was added, and the mixture allowed to stir for an additional 2 hours. The solution pH was then measured and adjusted to approximately pH 6 using 4 M sodium hydroxide solution. The reaction mixture was concentrated to dryness under reduced pressure, water (300 cm^3) added and then stirred for 30 minutes. After vacuum filtration and washing with water (200 cm^3), ethanol (100 cm^3) and dichloromethane (200 cm^3), *sulfonic acid* **65** (23.7 g, 70.9 mmol, 81 %) was isolated as a colourless powder, mp > 280 °C; $[\alpha]_D^{22}$ +24.4 (*c* 2.5 in $(CH_3)_2SO$); (Found: C, 40.7; H, 5.44; N, 7.8. $C_{12}H_{18}N_2O_5S_2.H_2O$ requires C, 40.9; H, 5.72; N, 7.95); ν_{max}(KBr disc)/cm^{-1} 3148 (NH_3^+), 2928 (H–C–H), 1990 & 1611 (NH_3^+), 1497 (C=C), 1331 (SO_2–N) and 1212 (SO_2–O); δ_H(300 MHz; D_2O) 7.91 (2H, d, *J* 8.9, Ar-*H*), 7.88 (2H, d, *J* 8.9, Ar-*H*), 3.02 (1H, ddd (app. td), *J* 10.9 and 4.5, CH_AH$_B$C), 2.88 (1H, ddd (app. td), *J* 10.9 and 4.0, CH$_A$$H_B$C), 1.99 – 1.89 (1H, m, Cy), 1.62 – 1.51 (1H, m, Cy), 1.46 – 1.21 (2H, m, Cy) and 1.19 – 0.84 (4H, m, Cy); δ_C(75.5 MHz; $(CD_3)_2SO$) 152.2 (C), 141.7 (C), 126.8 (CH), 126.6 (CH), 55.2 (CH), 53.7 (CH), 30.7 (CH_2), 29.4 (CH_2), 24.2 (CH_2) and 23.3

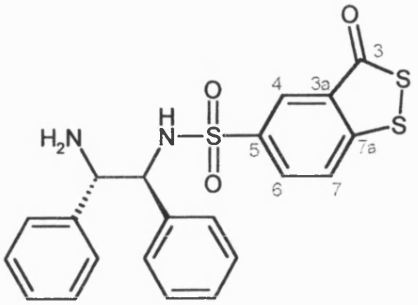
(CH_2); *m/z* (FAB-) 333.0584 (100 %, $[M\text{-}H^+]^-$ – $C_{12}H_{17}N_2O_5S_2$ requires 333.0579), 276 (41), 195 (36) and 106 (35).

3-Oxo-3*H*-1,2-benzodithiole-5-sulfonyl chloride (71)



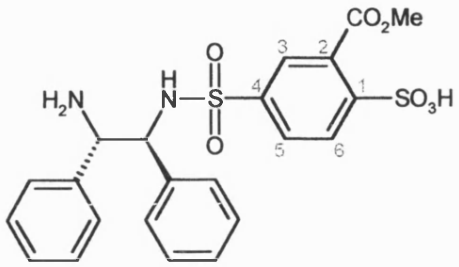
Chlorosulfonic acid (7.5 cm^3, 0.1 mol) in dichloromethane (20 cm^3) was added to a solution of 3*H*-1,2-benzodithiol-3-one (1.68 g, 10 mmol) in dichloromethane (30 cm^3). The mixture was heated at reflux for 20 hours, poured into crushed ice and then allowed to warm to room temperature. The *product* was extracted with dichloromethane (3 x 60 cm^3), and the combined extracts washed once with concentrated sodium hydrogencarbonate solution (100 cm^3) and then dried over anhydrous sodium sulfate. Evaporation under reduced pressure yielded an orange solid. Crystallisation from diethyl ether gave 3-oxo-3*H*-1,2-benzodithiole-5-sulfonyl chloride **71** (1.2 g, 4.5 mmol, 45 %) as orange/yellow cubes, mp 97 – 98 °C; (Found: C, 31.3; H, 1.15. $C_7H_3ClO_3S_3$ requires C, 31.5; H, 1.13); ν_{max}(KBr disc)/cm^{-1} 3088 (aryl–H), 1664 (C=O), 1581 (C=C), 1377 & 1187 (SO_2–Cl) and 1167 (O=S=O); δ_H(400 MHz; $CDCl_3$) 8.56 (1H, d, *J* 1.9, H-4), 8.22 (1H, dd, *J* 8.7 and 1.9, H-6) and 7.88 (1H, d, *J* 8.7, H-7); δ_C(100.5 MHz; $CDCl_3$) 190.8 (C-3), 154.9 (C), 142.2 (C), 130.3 (CH), 130.1 (C), 127.1 (CH) and 126.4 (CH); *m/z* (FAB+) 266.9001 (50 %, $[MH]^+$ – $C_7H_4ClO_3S_3$ requires 266.9011), 133 (42), 111 (59) and 97 (100).

_N_-[(1_S_,2_S_)-2-amino-1,2-diphenylethyl]-3-oxo-3_H_-1,2-benzodithiole-5-sulfonamide (72)



3-Oxo-3*H*-1,2-benzodithiole-5-sulfonyl chloride **71** (0.47 g, 1.76 mmol) in dichloromethane (10 cm^3) was added dropwise to a solution of (1*S*,2*S*)-(-)-1,2-diphenylethylenediamine (0.41 g, 1.93 mmol) and triethylamine (0.65 cm^3, 0.47 g, 4.6 mmol) in dichloromethane (20 cm^3) at 0 °C. The reaction mixture was stirred for 2 hours at room temperature, and then concentrated to dryness under reduced pressure. The crude material was redissolved in dichloromethane and purified by column chromatography (SiO_2, CH_2Cl_2/MeOH – 185:15, detection – UV and ninhydrin). *Sulfonamide* **72** (0.65 g, 1.47 mmol, 83 %) was obtained as a pale yellow powder, mp 144 – 145 °C; $[\alpha]_D^{22}$ +35 (*c* 2 in CH_2Cl_2); ν_{max}(KBr disc)/cm^{-1} 3351 & 3296 (N–H), 3060 (aryl–H), 1668 (C=O), 1585 (C=C), 1348 (SO_2–N) and 1155 (O=S=O); δ_H(270 MHz; $CDCl_3$) 8.06 (1H, d, *J* 1.7, H-4), 7.83 (1H, dd, *J* 8.4 and 1.7, H-6), 7.55 (1H, d, *J* 8.4, H-7), 7.43 – 7.22 (10H, m, Ph), 4.67 (1H, d, *J* 4.3, CH_AH_BC) and 4.41 (1H, d, *J* 4.3, CH_AH_BC); δ_C(100.5 MHz; $CDCl_3$) 191.2 (C-3), 151.2 (C), 140.9 (C), 138.9 (C), 138.3 (C), 130.5 (CH), 129.0 (C), 128.4 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 126.7 (CH), 126.12 (CH), 126.09 (CH), 124.5 (CH), 63.2 (CH) and 60.0 (CH); *m/z* (FAB+) 443.0567 (54 %, $[MH]^+$ – $C_{21}H_{19}N_2O_3S_3$ requires 443.0558), 196 (15) and 106 (100).

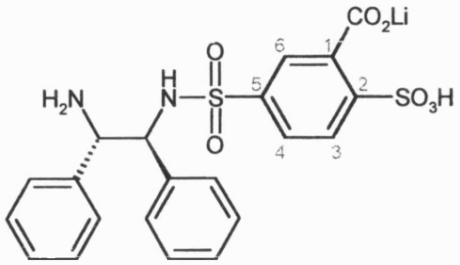
4-({[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]amino}sulfonyl)-2-(methoxycarbonyl) benzenesulfonic acid (73)



Sodium hydroxide (1.8 cm^3 of a 1 M solution in water, 1.8 mmol) and hydrogen peroxide (1 cm^3 of a 27.5 wt % solution in water) were added to a solution of sulfonamide **72** (0.20 g, 0.45 mmol) in methanol (20 cm^3). The resulting mixture was stirred for 2 hours before the addition of a further 1 cm^3 of hydrogen peroxide solution. After 12 hours stirring at room temperature, concentrated sodium hydrogen sulfite solution (2 cm^3) was added and the mixture allowed to stir for an additional 2 hours. The solution pH was then measured and adjusted to pH 6 using 1 M sodium hydroxide solution. The reaction mixture was concentrated to dryness under reduced pressure, water (25 cm^3) added and then stirred for 30 minutes. After vacuum filtration and washing with water (5 cm^3), ethanol (5 cm^3) and dichloromethane (20 cm^3), *sulfonic acid* **73** (98 mg, 0.20 mmol, 44 %) was isolated as a fine colourless powder, mp > 270 °C (decomposition); $[\alpha]_D^{22}$ -96 (*c* 1.15 in $(CH_3)_2SO$); (Found: C, 54.0; H, 4.72; N, 5.9. $C_{22}H_{22}N_2O_7S_2$ requires C, 53.9; H, 4.52; N, 5.7); ν_{max}(KBr disc)/cm^{-1} 3175 (SO_2N–H), 3066 (NH_3^+), 2014 (NH_3^+), 1735 (C=O), 1610 (NH_3^+), 1522 (C=C) and 1348 (SO_2–N); δ_H(300 MHz; $(CD_3)_2SO$) 8.57 (4H, br s, NH), 7.55 (1H, d, *J* 8.3, H-6), 7.43 (1H, dd, *J* 8.3 and 1.9, H-5), 7.29 (1H, d, *J* 1.9, H-3), 7.18 (5H, app. s, Ph), 6.96 – 6.74 (5H, m, Ph), 4.67 (1H, d, *J* 10.3, C$H_A$$H_B$C), 4.40 (1H, d, *J* 10.3, C$H_A$$H_B$C) and 3.68 (3H, s, Me); δ_C(100.5 MHz; $(CD_3)_2SO$) 167.7 (CO), 148.3 (C), 140.3 (C), 135.2 (C), 133.9 (C), 131.2

(C), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 124.8 (CH), 61.4 (CH), 58.3 (CH) and 52.1 (Me); *m/z* (ES-) 489.0801 (100 %, $[M\text{-}H^+]^-$ – $C_{22}H_{21}N_2O_7S_2$ requires 489.0790).

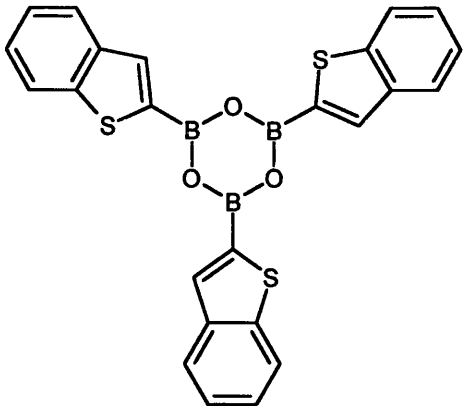
Lithium 5-({[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]amino}sulfonyl)-2-sulfobenzoate (66)



4-({[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]amino}sulfonyl)-2-(methoxycarbonyl)benzene sulfonic acid **73** (150 mg, 0.31 mmol) and lithium hydroxide monohydrate (52 mg, 1.2 mmol) were heated at reflux in a 2-propanol (10 cm^3) and water (0.2 cm^3) mixture for 22 hours. After cooling, solution pH was adjusted to approximately pH 7 by the dropwise addition of 2 M hydrochloric acid; this produced a colourless precipitate which was collected by vacuum filtration, washed with 2-propanol (10 cm^3) and dried at 50 °C overnight to give *diacid* **66** (140 mg, 0.29 mmol, 94 %) as a fine colourless powder, mp 268 – 269 °C; $[\alpha]_D^{22}$ -59 (*c* 1.09 in H_2O); ν_{max}(KBr disc)/cm^{-1} 3233 (SO_2N–H), 3060 (NH_3^+), 1957 (NH_3^+), 1630 (C=O), 1521 (C=C), 1404 (SO_2–O), 1368 (SO_2–N), and 1155 (O=S=O); δ_H(270 MHz; $(CD_3)_2SO$) 7.71 (1H, d, *J* 1.7, H-6), 7.63 (1H, d, *J* 7.8, H-3), 7.40 (1H, d, *J* 7.8, H-4), 7.16 – 7.04 (5H, m, Ph), 7.00 – 6.88 (5H, m, Ph), 4.42 (1H, d, *J* 7.8, CH_AH$_B$C) and 4.07 (1H, d, *J* 7.8, CH$_A$$H_B$C); δ_C(75.5 MHz; D_2O) 175.7 (CO), 143.0 (C), 141.7 (C), 140.7 (C), 135.3 (C), 133.7 (C), 130.7 (CH), 130.3 (CH), 129.8 (CH), 129.7 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 127.0 (CH), 126.4(CH), 62.2

(CH) and 59.9 (CH); *m/z* (ES-) 475.0646 (100 %, $[M\text{-}Li^+]^-$ – $C_{21}H_{19}N_2O_7S_2$ requires 475.0634).

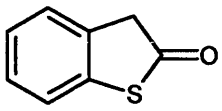
2,4,6-Tri(2-benzo[*b*]thienyl)cyclotriboroxane (76)[111]



A solution of *n*-butyllithium (65 cm^3 of a 2.5 M solution in hexane, 163 mmol) was added dropwise to a solution of benzo[*b*]thiophene (19.8 g, 147.5 mmol) in diethyl ether (220 cm^3) at 0 °C over a period of 30 – 40 minutes. The resulting mixture was allowed to reach room temperature and then stirred for 1 hour. Tributyl borate (48 cm^3, 178 mmol) in diethyl ether (50 cm^3) was then added during 10 minutes to the cooled (0 °C) mixture, and stirring continued at room temperature for 1 hour. Following the addition of hydrochloric acid (150 cm^3 of a 1 M solution in water) the organic phase was separated, and the aqueous phase extracted with diethyl ether (50 cm^3). The combined organic layers were then extracted with sodium hydroxide (75 cm^3 of a 2 M solution, followed by 50 cm^3 of a 1 M solution in water) and the basic aqueous extracts backwashed with diethyl ether (75 cm^3). Following acidification of the aqueous layer with concentrated hydrochloric acid, the product was extracted with diethyl ether (2 x 100 cm^3). Removal of solvent under reduced pressure gave boroxane **76** (22.4 g, 46.7 mmol, 95 %) as a pink-yellow solid, mp 252 – 256 °C (lit.,[111a] 259 – 260 °C); δ_H(300

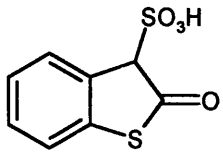
MHz; CD_3OD) 7.91 – 7.81 (3H, m, Ar-*H*) and 7.38 – 7.29 (2H, m, Ar-*H*); δ_C(75.5 MHz; $(CD_3)_2SO$) 142.9 (C), 141.1 (C), 131.4 (C), 125.0 (CH), 124.4 (CH) and 122.9 (CH).

Benzo[*b*]thiophen-2(3*H*)-one (75)[111a]



2,4,6-Tri(2-benzo[*b*]thienyl)cyclotriboroxane **76** (9.0 g, 18.8 mmol) was added slowly to a stirred solution of hydrogen peroxide (10 cm^3 of a 35 wt % solution in water) at such a rate that the temperature of the reaction mixture did not exceed 50 °C; gentle warming was required to initiate the reaction during the early stages of addition. The mixture was then heated to 70 °C for 15 minutes and allowed to cool to room temperature before the addition of water (20 cm^3). The product was extracted with dichloromethane (2 x 20 cm^3), and the combined extracts washed with water (3 x 20 cm^3) and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave a dark brown liquid, which on dissolution in hot petrol and cooling to -10 °C yielded benzo[*b*]thiophen-2(3*H*)-one **75** as yellow needle-like crystals (5.9 g, 39.3 mmol, 70 %), mp 32 – 34 °C (lit.,[111a] 34 – 35 °C); ν_{max}(film)/cm^{-1} 3063 (aryl–H), 1716 (C=O) and 1594 (C=C); δ_H(300 MHz; $CDCl_3$) 7.35 – 7.15 (4H, m, Ar-*H*) and 3.99 (2H, s, CH_2); δ_C(75.5 MHz; $CDCl_3$) 203.5 (CO), 137.5 (C), 132.6 (C), 128.8 (CH), 126.5 (CH), 125.2 (CH), 123.5 (CH) and 47.7 (CH_2).

2-Oxo-2,3-dihydro-1-benzothiophene-3-sulfonic acid (77)



Chlorosulfonic acid (9.4 cm^3 of a 0.3 M solution in dichloromethane, 2.8 mmol) was added dropwise to a solution of benzo[*b*]thiophen-2(3*H*)-one **75** (0.50 g, 3.3 mmol) in dichloromethane (20 cm^3) and diethyl ether (10 cm^3). The resulting mixture was heated at reflux for 15 minutes, cooled to room temperature and then poured into water (20 cm^3). After stirring for 30 minutes the aqueous phase was isolated and backwashed with diethyl ether (2 x 15 cm^3). Removal of solvent at 50 °C under reduced pressure yielded *sulfonic acid* **77** (0.46 g, 2.0 mmol, 71 %) as a light brown solid, ν_{max}(KBr disc)/cm^{-1} 3052 (aryl–H), 1710 (C=O), 1590 (C=C) and 1444 (SO_2–O); δ_H(400 MHz; $(CD_3)_2SO$) 7.54 (1H, d, *J* 7.6, Ar-*H*), 7.40 (1H, d, *J* 7.6, Ar-*H*), 7.29 (1H, dd (app. t), *J* 7.6, Ar-*H*), 7.19 (1H, ddd (app. td), *J* 7.6 and 1.2, Ar-*H*) and 4.89 (1H, s, ArC*H*SO_3H); δ_C(75.5 MHz; $(CD_3)_2SO$) 198.4 (CO), 136.4 (C), 133.5 (C), 128.7 (CH), 127.8 (CH), 125.8 (CH), 122.6 (CH) and 74.9 (CH); *m/z* (FAB+) 230.9790 (40 %, $[MH]^+$ – $C_8H_7O_4S_2$ requires 230.9786); *m/z* (FAB-) 229 (100 %, $[M\text{-}H^+]^-$), 149 (10) and 97 (15).

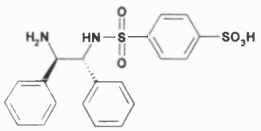
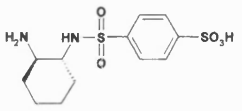
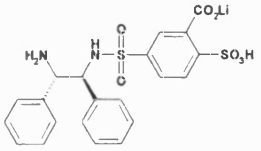
3.3 Ligand Titration Procedure

4-({[(1*R*,2*R*)-2-aminocyclohexyl]amino}sulfonyl)benzenesulfonic acid **65** (167 mg, 0.5 mmol) was dissolved in sodium hydroxide (50 cm^3 of a 0.01 M solution in water, 0.5 mmol) and the solution pH measured using a pH meter. Following the addition of hydrochloric acid (0.1 cm^3 of a 0.333 M solution in water, 0.033 mmol) the solution was allowed to stir for several minutes and the pH measured again. This process was repeated until thirty, 0.1 cm^3 aliquots of hydrochloric acid (0.333 M) had been added.

3.4 Typical Transfer Hydrogenation Procedures

Procedure A: Transfer hydrogenation under homogeneous conditions

A solution of potassium *tert*-butoxide in 2-propanol (0.8 cm^3 of a 0.1 M solution, 0.08 mmol) was added to a suspension of ligand (0.08 mmol, 4.0 mol%) in water (1.0 cm^3) and stirred at room temperature until a clear solution was obtained. To this solution, was added the catalyst precursor (0.01 mmol, 0.5 mol%) and the mixture stirred under argon at 40 °C for two hours. After cooling to room temperature, acetophenone (240 mg, 2.0 mmol) in 2-propanol (10 cm^3) was then added, along with water (1 cm^3) and potassium *tert*-butoxide (2.0 cm^3 of a 0.1 M solution in 2-propanol, 0.20 mmol). This mixture was stirred at room temperature under a stream of argon or nitrogen. Samples (approximately 0.05 cm^3) were taken out of the reaction mixture after a given time, passed through a small column of silica using diethyl ether (3 x 1 cm^3) as eluent and finally concentrated to approximately 0.5 cm^3. Percentage conversion to the corresponding alcohol and enantiomeric excess were determined by GC analysis. Configuration was established from the sign of rotation of the isolated product.

	Catalyst precursor or ligand	Mass (mg)
	Dichloro(*p*-cymene)ruthenium(II) dimer*	6.1
	Pentamethylcyclopentadienylrhodium(III) chloride dimer*	6.2
	Pentamethylcyclopentadienyliridium(III) chloride dimer*	8.0
ent-56		34.6
65		26.8
66		38.6

Catalyst precursor and ligand masses used for transfer hydrogenation procedure. * As listed in Aldrich catalogue.

Removal of the catalyst from homogeneous transfer hydrogenation reactions

Upon completion of reaction, all volatiles were removed under reduced pressure and water (25 cm^3) added. The mixture was then extracted with hexane (2 x 25 cm^3) and the organic layers combined and dried over sodium sulfate. After removal of solvent under reduced pressure the residue was submitted for analysis by ICP-MS.

Procedure B: Transfer hydrogenation under biphasic conditions

A solution of potassium *tert*-butoxide in 2-propanol (0.8 cm^3 of a 0.1 M solution, 0.08 mmol) was added to a suspension of ligand (0.08 mmol, 4.0 mol%) in water (1.0 cm^3) and stirred at room temperature until a clear solution was obtained. To this solution, was added the catalyst precursor (0.01 mmol, 0.5 mol%) and the mixture stirred under argon at 40 °C for two hours. After cooling to room temperature, acetophenone (240 mg, 2.0 mmol) in hexane (7 cm^3) was then added, along with water (5 cm^3) and potassium *tert*-butoxide (2.0 cm^3 of a 0.1 M solution in 2-propanol, 0.20 mmol). This mixture was then stirred vigorously at room temperature. Each biphasic reaction was performed in duplicate. From the first reaction mixture, samples (approximately 0.05 cm^3) of the upper hexane phase were removed periodically, passed through a small column of silica using diethyl ether (3 x 1 cm^3) as eluent, and finally concentrated to approximately 0.5 cm^3. Percentage conversion to the corresponding alcohol and enantiomeric excess were determined by GC analysis. The second reaction mixture was prepared for ruthenium level analysis as follows. At the end of the reaction, the phases were allowed to separate and the upper hexane phase removed. After the addition of sodium chloride (0.5 – 1 g), the aqueous phase was extracted with hexane (5 cm^3) and the organic layers combined. All volatiles were removed under reduced pressure and the residue submitted for analysis by ICP-MS.

Preparation of supported aqueous phase (SAP) catalyst (88)

Potassium *tert*-butoxide (3.2 cm^3 of a 0.1 M solution in 2-propanol, 0.32 mmol) was added to a suspension of 4-({[(1*R*,2*R*)-2-aminocyclohexyl]amino}sulfonyl)benzene sulfonic acid **65** (107 mg, 0.32 mmol) in water (20 cm^3) and 2-propanol (5 cm^3). Stirring at room temperature was continued until a clear solution had formed and then controlled pore glass (CPG 500 Å, 1000 mg) was added. This mixture was deoxygenated by purging with argon for 15 minutes, before the introduction of dichloro(*p*-cymene)ruthenium(II) dimer (50 mg, 0.08 mmol). After stirring at 40 °C for 2 hours, the mixture was concentrated to dryness under reduced pressure. The supported catalyst (1.1 g) was collected as a fine green powder with an approximate ruthenium loading of 0.14 mmol/g of supported catalyst.

Procedure C: Transfer hydrogenation using SAP catalyst 88

SAP catalyst **88** (140 mg, equivalent to 0.02 mmol Ru, 1 mol%) was weighed into a vial and oxygen removed by purging with argon. A mixture of acetophenone (240 mg, 2.0 mmol), potassium *tert*-butoxide (2.0 cm^3 of a 0.1 M solution in 2-propanol, 0.20 mmol), 2-propanol (4.5 cm^3) and hexane (6.5 cm^3) was then introduced, and the reaction mixture stirred at room temperature. Each reaction was performed in duplicate. From the first reaction mixture, samples (approximately 0.05 cm^3) were taken after allowing time for the catalyst to settle. The sample was filtered through a plug of silica, using diethyl ether (3 x 1 cm^3) as eluent and then concentrated before GC analysis. At the end of reaction, the second mixture was centrifuged and the supernatant liquid removed. The catalyst was then washed with hexane (5 cm^3), the mixture centrifuged and decanted. The combined reaction liquor and hexane wash were finally concentrated under reduced pressure and submitted for analysis by ICP-MS.

3.5 Biphasic Heck Coupling Procedure[84a]

Palladium chloride (17.7 mg, 0.10 mmol, 1 mol%) and disodium 3-[phenyl(3-sulfonatophenyl)phosphino]benzenesulfonate (103 mg, 0.22 mmol, 2.2 mol%) were dissolved in ethylene glycol (0.5 cm^3) under a nitrogen atmosphere. The solution was stirred at 60 °C for 1 hour before diluting with ethylene glycol (10 cm^3). To this solution, was added a mixture of toluene (10 cm^3), iodobenzene (1.12 cm^3, 2.04 g, 10 mmol), methyl acrylate (0.90 cm^3, 0.86 g, 10 mmol) and sodium acetate (0.82 g, 10 mmol) and the reaction mixture vigorously stirred at 140 °C in a pressure tube. After a 20 hour reaction time, the toluene phase was isolated and the ethylene glycol phase re-extracted with toluene (5 cm^3). The combined extracts were then either:

(a) Concentrated under reduced pressure and the product purified by column chromatography (SiO_2, petrol/diethyl ether – 3:1, detection – UV) to afford methyl *trans*-cinnamate (1.46 g, 9.0 mmol, 90 %) as a creamy white solid, mp 35 – 37 °C, ν_{max}(film)/cm^{-1} 2950 (CH_3), 1714 (C=O) and 1637 (C=C); δ_H(300 MHz; $CDCl_3$) 7.78 (1H, d, *J* 16.0, PhC*H*=CH), 7.55 – 7.48 (2H, m, Ph), 7.42 – 7.34 (3H, m, Ph), 6.44 (1H, d, *J* 16.0, CH=C*H*CO_2Me) and 3.81 (3H, s, Me); δ_C(75.5 MHz; $CDCl_3$) 167.8 (CO), 145.3 (Ph*C*H=CH), 134.8 (C), 130.7 (CH), 129.3 (CH), 128.5 (CH), 118.2 (CH=*C*HCO_2Me) and 52.1 (Me).

(b) Prepared for palladium leaching measurements as follows: All volatiles were removed using a heat gun, 6 drops of aqua regia (concentrated hydrochloric acid/concentrated nitric acid – 3:1) added and the mixture stirred for 30 minutes. Following the addition of deionised water (5 cm^3), the sample was sonicated in an ultrasound bath for 20 minutes and finally centrifuged. The supernatant liquid was submitted for atomic absorption analysis.

References

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118. Publications which have resulted from the work described in this thesis are given in the Appendix, p 145.

119. Determined from the sign of rotation of the isolated product. For specific rotation values see: Nakamura, K.; Matsuda, T. *J. Org. Chem.* **1998**, *63*, 8957-8964

Appendix

CRYSTAL DATA AND STRUCTURE REFINEMENT FOR 71

Identification code	k00jmjw4 (relabelled)
Empirical formula	$C_7H_3ClO_3S_3$
Formula weight	266.72
Temperature	170(2) K
Wavelength	0.71070 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.1280(2)Å α = 97.607(2)°
	b = 7.4960(2)Å β = 110.422(2)°
	c = 9.7430(3)Å γ = 95.823(2)°
Volume	477.42(2) $Å^3$
Z	2
Density (calculated)	1.855 Mg/m^3
Absorption coefficient	1.028 mm^{-1}
F(000)	268
Crystal size	0.28 x 0.25 x 0.10 mm
Theta range for data collection	3.81 to 27.52°
Index ranges	-9<=h<=9; -9<=k<=9; -12<=l<=12
Reflections collected	6556
Independent reflections	2182 [R(int) = 0.0289]
Reflections observed (>2σ)	2039
Data Completeness	0.990
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.04 and 0.95
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2182 / 0 / 128
Goodness-of-fit on F^2	1.087
Final R indices [I>2σ(I)]	R_1 = 0.0231 wR_2 = 0.0621
R indices (all data)	R_1 = 0.0252 wR_2 = 0.0634
Largest diff. peak and hole	0.317 and -0.423 $eÅ^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Cl(1)	7931(1)	452(1)	10915(1)	28(1)
S(1)	8617(1)	2963(1)	10470(1)	17(1)
S(2)	2764(1)	2504(1)	3914(1)	23(1)
S(3)	5019(1)	2284(1)	3059(1)	24(1)
O(1)	8043(2)	4210(2)	11428(1)	26(1)
O(2)	10668(1)	3125(1)	10548(1)	23(1)
O(3)	8751(2)	2148(2)	4813(1)	37(1)
C(3)	7055(2)	2269(2)	4774(2)	22(1)
C(3A)	6368(2)	2430(2)	6038(2)	17(1)
C(4)	7707(2)	2506(2)	7494(2)	18(1)
C(5)	6958(2)	2761(2)	8621(2)	16(1)
C(6)	4916(2)	2925(2)	8348(2)	19(1)
C(7)	3594(2)	2813(2)	6911(2)	20(1)
C(7A)	4335(2)	2567(2)	5750(2)	17(1)

Bond lengths [Å] and angles [°] for 1.

Cl(1)-S(1)	2.0362(5)	S(1)-O(1)	1.4240(10)
S(1)-O(2)	1.4283(10)	S(1)-C(5)	1.7523(13)
S(2)-C(7A)	1.7396(13)	S(2)-S(3)	2.0628(5)
S(3)-C(3)	1.7929(15)	O(3)-C(3)	1.2091(18)
C(3)-C(3A)	1.4714(19)	C(3A)-C(7A)	1.3943(18)
C(3A)-C(4)	1.3966(19)	C(4)-C(5)	1.3786(19)
C(5)-C(6)	1.4074(18)	C(6)-C(7)	1.374(2)
C(7)-C(7A)	1.4042(19)		
O(1)-S(1)-O(2)	120.67(7)	O(1)-S(1)-C(5)	110.26(6)
O(2)-S(1)-C(5)	110.26(6)	O(1)-S(1)-Cl(1)	105.72(5)
O(2)-S(1)-Cl(1)	106.39(5)	C(5)-S(1)-Cl(1)	101.62(5)
C(7A)-S(2)-S(3)	95.13(5)	C(3)-S(3)-S(2)	97.61(5)
O(3)-C(3)-C(3A)	127.11(13)	O(3)-C(3)-S(3)	121.45(11)
C(3A)-C(3)-S(3)	111.43(10)	C(7A)-C(3A)-C(4)	120.31(12)
C(7A)-C(3A)-C(3)	117.98(12)	C(4)-C(3A)-C(3)	121.68(12)
C(5)-C(4)-C(3A)	117.82(12)	C(4)-C(5)-C(6)	122.44(12)
C(4)-C(5)-S(1)	119.11(10)	C(6)-C(5)-S(1)	118.42(10)
C(7)-C(6)-C(5)	119.55(12)	C(6)-C(7)-C(7A)	118.76(12)
C(3A)-C(7A)-C(7)	121.11(12)	C(3A)-C(7A)-S(2)	117.83(10)
C(7)-C(7A)-S(2)	121.02(10)		

Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

Atom	U11	U22	U33	U23	U13	U12
Cl(1)	30(1)	25(1)	27(1)	10(1)	5(1)	1(1)
S(1)	16(1)	19(1)	13(1)	1(1)	3(1)	3(1)
S(2)	18(1)	33(1)	16(1)	5(1)	2(1)	7(1)
S(3)	22(1)	35(1)	15(1)	4(1)	6(1)	3(1)
O(1)	30(1)	29(1)	18(1)	-2(1)	8(1)	8(1)
O(2)	16(1)	30(1)	19(1)	3(1)	3(1)	3(1)
O(3)	20(1)	69(1)	24(1)	4(1)	11(1)	7(1)
C(3)	18(1)	30(1)	16(1)	1(1)	5(1)	1(1)
C(3A)	17(1)	18(1)	16(1)	2(1)	5(1)	2(1)
C(4)	13(1)	22(1)	17(1)	1(1)	4(1)	2(1)
C(5)	16(1)	16(1)	15(1)	2(1)	3(1)	2(1)
C(6)	17(1)	22(1)	18(1)	3(1)	7(1)	4(1)
C(7)	14(1)	25(1)	21(1)	4(1)	6(1)	5(1)
C(7A)	16(1)	17(1)	16(1)	3(1)	3(1)	2(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(4)	9089	2386	7702	22
H(6)	4453	3112	9152	22
H(7)	2206	2900	6705	24

PUBLICATIONS

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TETRAHEDRON LETTERS

A practical synthesis of a disulfonated phosphine and its application to biphasic catalysis

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Received 16 March 2000; accepted 20 April 2000

Abstract

A convenient synthesis of TPPDS (disodium P-phenyl-3,3′-phosphinediyl-bis(benzenesulfonate)) from triphenylphosphine is described. This represents a quick and reliable way to prepare a water-soluble phosphine with essentially no phosphine oxide formation. © 2000 Published by Elsevier Science Ltd.

Complexes of water-soluble phosphines have attracted considerable interest since the development of the Ruhrchemie/Rhône-Poulenc biphasic hydroformylation process.[1] TPPTS [P(*m*-$C_6H_4SO_3Na)_3$] was utilised in this process and is the most commonly used phosphine ligand for the preparation of water-soluble organometallic complexes.[2] The preparation of TPPTS is not trivial; this is demonstrated by the number of communications for its synthesis.[3] Often the synthetic procedures are cumbersome and difficult to reproduce because of the formation of phosphine oxide during the reaction. Herein, we report on the synthesis of TPPDS [(C_6H_5)P(*m*-$C_6H_4SO_3Na)_2$] **1**, a water-soluble phosphine that can be prepared without the formation of phosphine oxide (Scheme 1). The procedure is straightforward, quick and reliable.

Triphenylphosphine[4] (3.0 g, 11.4 mmol) and concentrated sulfuric acid (21 cm^3) were placed in a 500 cm^3 round-bottomed flask and stirred at room temperature until dissolution.[5] The solution was then cooled to 0°C before the slow addition of oleum (9.5 cm^3, 65 wt% SO_3). The flask was then sealed and the mixture stirred at room temperature for 21 hours. The neutralisation was carried out at 0°C by the slow, dropwise addition of NaOH (157 cm^3, 7.5 M).[6] The mixture, now containing crystalline sodium sulfate was then transferred to a 1000 cm^3 round-bottomed flask

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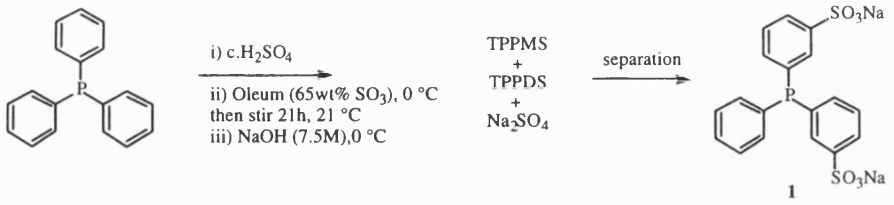
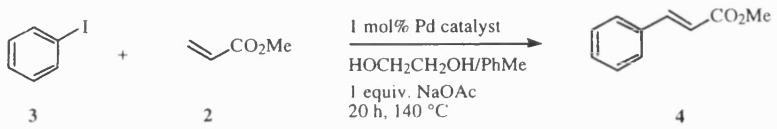


Scheme 1.

and most of the water removed under vacuum. The remaining solid was refluxed in methanol (300 cm^3) for 30 min and the solution filtered hot to remove the sodium sulfate. The methanol and residual water were removed under vacuum yielding a white solid. Dissolution of this solid in hot methanol (300 cm^3) followed by the addition of ethyl acetate (850 cm^3) caused the precipitation of TPPDS·$2H_2O$ on standing. Yield: 3.45 g (60%).

The utility of TPPDS is demonstrated in a biphasic palladium-catalysed Heck reaction.[7] TPPTS and TPPMS [$(C_6H_5)_2P(m\text{-}C_6H_4SO_3Na)$] were also used for comparison. Methyl acrylate **2** and iodobenzene **3** were treated with the prepared palladium catalyst in the presence of sodium acetate (Scheme 2).



Ligand	Isolated yield of 4 (%)	Pd leaching[8] (ppm, %)
TPPMS	85	3.5, 0.3
TPPDS	88	1.8, 0.2
TPPTS	87	2.3, 0.2

Scheme 2.

The results show that each catalyst is effective in the formation of methyl cinnamate **4**. Leaching levels are also comparable; the percentage leaching represents the amount of palladium contamination with respect to the amount of palladium catalyst employed.[8] TPPDS is readily accessible by this reported method and performs as well as TPPTS in biphasic palladium-catalysed Heck reactions.

Acknowledgements

We wish to thank AstraZeneca for the funding for this project.

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4. Triphenylphosphine was recrystallised from hot methanol before use.
5. Protonation of the phosphine provides stability against the oxidising nature of the oleum.
6. The addition of NaOH should take no less than 1 hour due to the exothermic nature of the reaction. It is at this stage that oxidation of the phosphorus is likely to occur. During the early stages of neutralisation the solution still has the potential to oxidise and oxidation is more likely at elevated temperatures.
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8. Leaching of palladium was determined as follows: The toluene phase was removed and all volatiles evaporated. The samples were then extracted with aqua regia (3:1 cHCl:cHNO_3, 0.2 cm^3). Deionised water (5 cm^3) was then added and the samples centrifuged. Analysis was undertaken on a Perkin–Elmer 1100B atomic absorption instrument in conjunction with a series of Pd standards.

Pergamon

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TETRAHEDRON LETTERS

Synthesis of water-soluble aminosulfonamide ligands and their application in enantioselective transfer hydrogenation

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Abstract—Water-soluble analogues of Noyori's (1*S*,2*S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine and Knochel's (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diaminocyclohexane, containing an additional sulfonic acid group, have been synthesised. The ruthenium catalysed reduction of aromatic ketones using enantiomerically pure catalyst derived from water soluble ligands and $[RuCl_2(p\text{-cymene})]_2$ has been examined. High enantioselectivity and moderate activity were observed in the 2-propanol/base system. The addition of water is necessary to stabilise the catalyst.

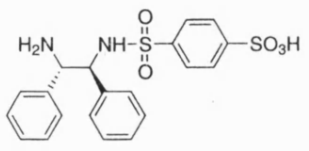
1. Introduction

Enantioselective transfer hydrogenation reactions of prochiral ketones have been achieved using a range of catalysts.[1] Amongst the best catalysts for these reactions are ruthenium complexes developed by Noyori[2] and Knochel.[3]

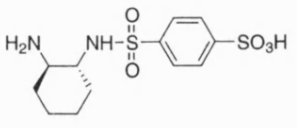
There has been considerable interest in the development of water-soluble ligands,[4] which allow metal catalysed reactions to take place in water,[5] other polar solvents, biphasic systems[6] and in supported polar phase catalysis.[7] We are interested in preparing water-soluble ligands, which would be effective in the enantioselective transfer hydrogenation of ketones. In this Letter, we report the successful synthesis of ligands **1**, **2** and **3** and their use in asymmetric catalysis.

2. Results and discussion

Ligand **1** was prepared as shown in Scheme 1. Sulfanilic acid **4** was first converted to the sodium salt of 4,4-dithiobisbenzenesulfonic acid **5** using a procedure previously described by Smith et al.[8] via diazotisation followed by quenching with disodium disulfide. The conversion of compound **5** into bissulfochloride **6** was effected using a mixture of PCl_5 and $POCl_3$ at reflux. Addition of (1*S*,2*S*)-diphenylethylenediamine (DPEN) **7** to a solution of **6** in (10:1) dichloromethane/triethylamine gave bissulfonamide **8** in high yield. Oxidation of



1



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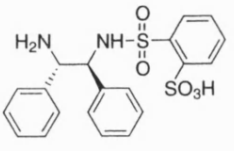

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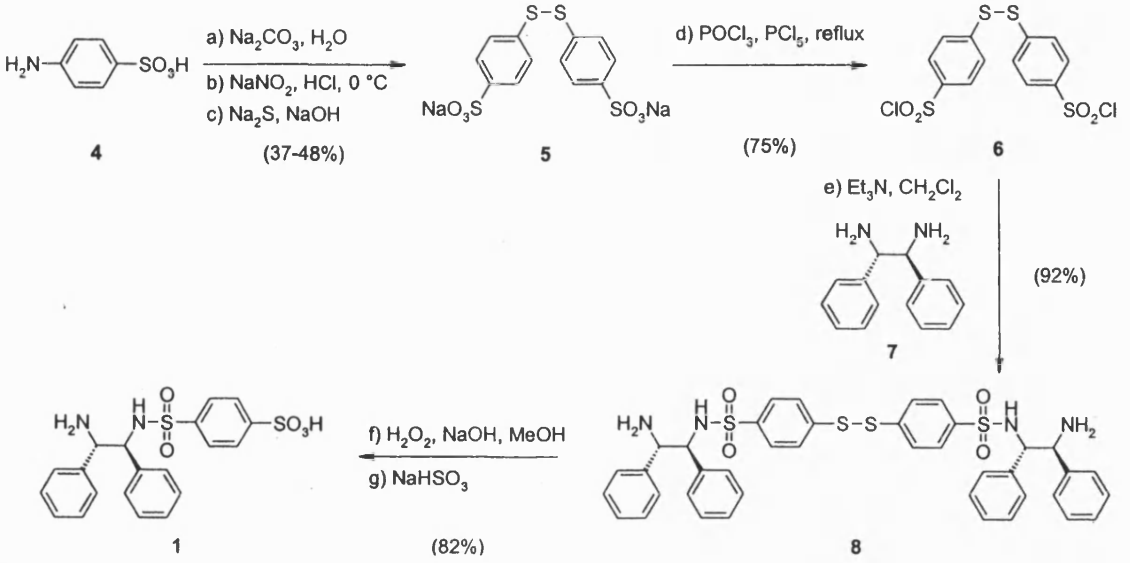
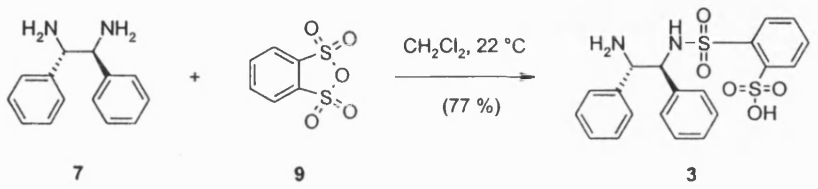
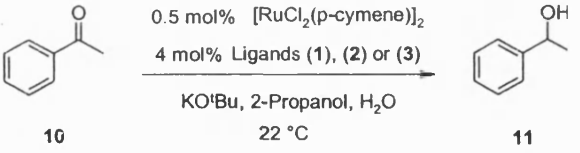


Scheme 1.



Scheme 2.

the disulfide bond with basic hydrogen peroxide produced ligand **1** in good yield. Ligand **2** was prepared in a similar manner using (1*R*,2*R*)-diaminocyclohexane in place of DPEN. As expected, ligand **2** has a higher water-solubility than ligand **1**. As a result of this a slightly lower yield was isolated.



Scheme 3.

12 **13** **14** **15**

Table 1. Asymmetric transfer hydrogenation of aromatic ketones catalysed by polar ruthenium complexes

Ketone	Ligand	Reaction time (h)	Conversion (%)	Enantiomeric excess (%)	Configuration
10	**1**	48	96	94	*S*
10	**2**	48	91	88	*R*
10	**3**	48	11	91	*S*
12	**1**	72	94	95	*S*
12	**2**	48	87	90	*R*
13	**1**	4	100	81	*S*
13	**2**	4	100	88	*R*
14	**1**	24	90	87	*S*
14	**2**	24	91	81	*R*
15	**1**	42	31	91	*S*
15	**2**	42	35	83	*R*

Ligand **3** was prepared in one-step by the reaction of (1*S*,2*S*)-diphenylethylenediamine **7** with benzene-1,2-disulfonic acid anhydride[9] **9** as shown in Scheme 2.

The water-soluble amino sulfonic acid ligands **1**, **2** and **3** were tested in the ruthenium catalysed transfer hydrogenation using 2-propanol as the source of hydrogen. The enantiomerically pure ruthenium catalyst was prepared by reacting $[RuCl_2(p\text{-cymene})]_2$ with the required ligand in the presence of base at 40°C. Under standard conditions,[10] acetophenone **10** was converted into phenethyl alcohol **11** (Scheme 3). The aromatic ketones **12**, **13**, **14** and **15** were also reduced to the corresponding alcohols under identical conditions (Table 1).

Preliminary results indicate that ruthenium ligand **1** systems give rise to a higher enantioselectivity, whilst ruthenium ligand **2** systems demonstrate higher activity. As yet, little work has been carried out using ligand **3**; however, crystalline transition metal complexes of this ligand have been isolated and characterised by X-ray crystallography. As expected, electron deficient ketones **13** and **14** were reduced more rapidly than the electron rich ketone **15**.

In summary, the preparation of three new water-soluble ligands has been achieved. Initial experiments demonstrate that these function are effective chiral ligands in the reduction of various aromatic ketones under transfer hydrogenation conditions. It is anticipated that these ligands will enable the development of biphasic systems and ultimately, supported liquid phase catalysts. Our attention will now turn to this chemistry and results will be reported in due course.

Acknowledgements

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TETRAHEDRON LETTERS

Efficient rhodium and iridium-catalysed asymmetric transfer hydrogenation using water-soluble aminosulfonamide ligands

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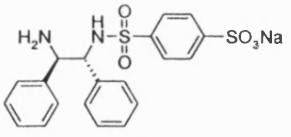
Abstract—A range of aromatic ketones was reduced asymmetrically under transfer hydrogenation conditions using enantiomerically pure catalysts derived from water-soluble diamine ligands and $[Cp^*MCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl, M = Rh, Ir). High catalytic activity and enantioselectivity were observed in systems containing up to 51% water.

1. Introduction

Asymmetric catalytic transfer hydrogenation using 2-propanol as a source of hydrogen is an attractive method for the preparation of chiral alcohols and amines.[1] The majority of work carried out in this area has used ruthenium catalysts in combination with a variety of phosphine and amine ligands.[2] Of these, the most notable transfer hydrogenation system incorporates the Ru(II)–TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) catalyst, first reported by Noyori et al.[3] More recently, the synthesis and application of efficient rhodium-based catalysts has been reported in the literature.[4] Whilst the utility of irridium catalysts for transfer hydrogenation has been documented, there are few results that compare with those obtained from ruthenium or rhodium-based systems.[4b,5]

Recently, we have used the water-soluble aminosulfonic acid ligands **1** and **2** with ruthenium for the transfer reduction of various aromatic ketones.[6] Herein, we report on the synthesis and application of efficient water-soluble rhodium and iridium-based catalysts for asymmetric transfer hydrogenation under aqueous conditions. Our research interests lie in the area of supported liquid phase (SLP) catalysis[7] and this work is a step further in the development of a SLP transfer hydrogenation catalyst.



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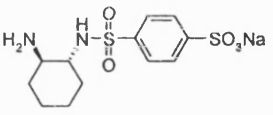

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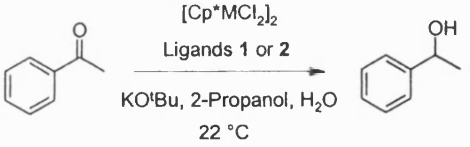
2. Results and discussion

The chiral rhodium or iridium complexes were prepared by reacting $[Cp^*MCl_2]_2$ (M = Rh, Ir) with ligands **1** or **2** in the presence of base at 40°C ($[Cp^*MCl_2]_2$/diamine/



Scheme 1.

* Corresponding author.

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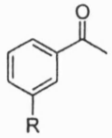
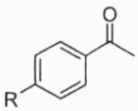
PII: S0040-4039(01)00624-4

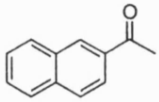
Table 1. Asymmetric transfer hydrogenation of acetophenones catalysed by polar rhodium complexes



3: R=H, **4**: R=CF_3, **5**: R=F



6: R=OMe, **7**: R=Br



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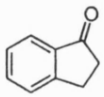

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Ketone	Ligand	Reaction time (h)	Conversion (%)	Enantiomeric excess (%)	Configuration
3	**1**	24	92	97	*R*
	2	18	94	95	*R*
4	**1**	18	98	95	*R*
	2	4	99	94	*R*
6	**1**	42	9	94	*R*
	2	42	65	95	*R*
8	**1**	64	81	82	*R*
	2	48	95	96	*R*

Table 2. Asymmetric transfer hydrogenation of acetophenones catalysed by polar iridium complexes

Ketone	Ligand	Reaction time (h)	Conversion (%)	Enantiomeric excess (%)	Configuration
3	**1**	140	90	82	*R*
	2	26	88	96	*R*
4	**1**	43	95	86	*R*
	2	4	98	93	*R*
5	**1**	51	83	85	*R*
	2	26	99	94	*R*
6	**1**	150	22	78	*R*
	2	141	80	95	*R*
7	**1**	91	93	76	*R*
	2	20	99	95	*R*
8	**1**	139	77	73	*R*
	2	45	96	96	*R*
9	**1**	139	41	91	*R*
	2	45	55	97	*R*

base = 1:8:8) and were used immediately without isolation.[8] A range of aromatic ketones was reduced at room temperature under transfer hydrogenation conditions (Scheme 1). Tables 1 and 2 show the results from systems containing 15% water.

Both the choice of metal and ligand affected the rate and enantioselectivity of the reaction in the expected manner.[2] Rhodium-based complexes proved to be superior catalysts in terms of rate and enantioselectivity, with ligand **2** systems providing higher reactivity. The electronic properties of the substrate had a significant effect on the outcome of the reaction. Electron deficient ketones were reduced rapidly to the corresponding alcohols with high conversion and enantioselectivity. Electron-rich ketones were reduced more slowly but also with high enantioselectivity.

In order to determine the effect of an increase in water concentration, the iridium-catalysed transfer hydrogenation experiments were carried out in a 2-propanol–water mixture containing 34 and 51% water. The overall volume of reaction solvent remained unchanged. The results (Table 3) were quite surprising. An expected rate decrease relating to the lower concentration of 2-propanol was not seen. Instead, a significant rate increase was noted for both systems. In addition to this, a large increase in enantiomeric excess was observed for ligand **1** systems when the concentration of water was increased from 15 to 34%. The reason for these results is not clear at this time.

In conclusion, we have used water-soluble rhodium and iridium complexes to efficiently catalyse the asymmetric reduction of various aromatic ketones. Our future work will concentrate on the development of biphasic and supported liquid phase systems that utilise these catalysts.

Acknowledgements

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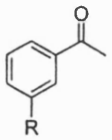
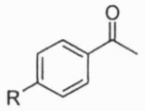
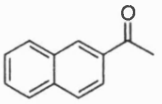
Table 1. Asymmetric transfer hydrogenation of acetophenones catalysed by polar rhodium complexes



3: R=H, **4**: R=CF_3, **5**: R=F



6: R=OMe, **7**: R=Br



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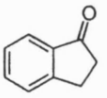

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Acknowledgements

We wish to thank AstraZeneca for the funding for this project through the strategic research fund.

Table 3. Transfer hydrogenation using iridium catalysts in systems containing (i) 34% and (ii) 51% water

Ketone	Ligand	Reaction time (h)		Conversion (%)	Enantiomeric excess (%)
5	**1**	22	(i)	74	92
			(ii)	90	92
5	**2**	2.5	(i)	82	94
			(ii)	94	93
6	**1**	115	(i)	20	91
			(ii)	33	92
6	**2**	116	(i)	76	92
			(ii)	89	87
8	**1**	42	(i)	47	91
			(ii)	66	93
8	**2**	18	(i)	92	95
			(ii)	92	94

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8. A solution of potassium *tert*-butoxide in isopropanol (0.8 cm^3 of a 0.1 M solution, 0.08 mmol) was added to a suspension of ligand (**1**) (34.6 mg, 0.08 mmol) in water (1 cm^3) and stirred at room temperature until a clear solution was obtained. To this solution $[Cp^*IrCl_2]_2$ (8.0 mg, 0.01 mmol) was added and the mixture stirred under argon at 40°C for 2 hours and then allowed to cool to room temperature. Acetophenone (240 mg, 2 mmol) in isopropanol (10 cm^3) was then added along with water (1 cm^3) and potassium *tert*-butoxide in isopropanol (2 cm^3 of a 0.1 M solution, 0.20 mmol). This mixture was then stirred at 22°C. Samples (approx. 0.05 cm^3) were taken out of the reaction mixture after the given time, passed through a small column of silica using Et_2O (3×1 cm^3) as the eluent and finally concentrated to approx. 0.5 cm^3. Analysis was undertaken by GC using a Supelco beta-dex 120 column. Configuration was determined from the sign of rotation of the isolated product.

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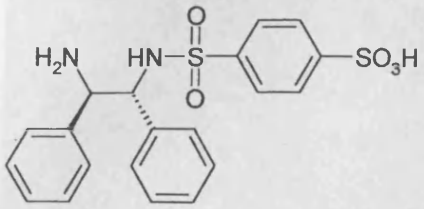

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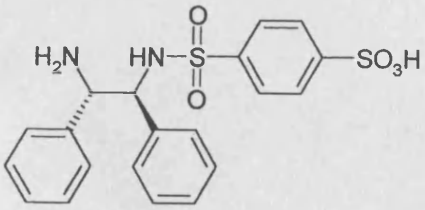

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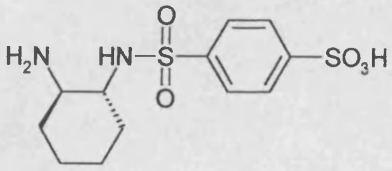

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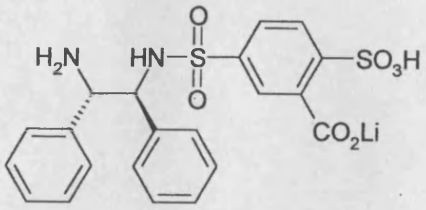

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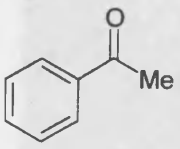
SUBSTRATES



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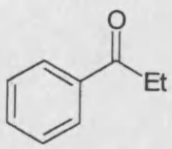

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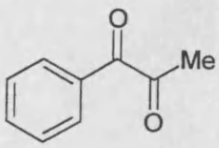

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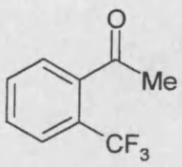

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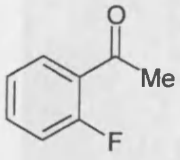

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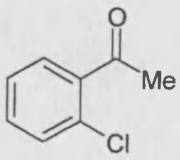

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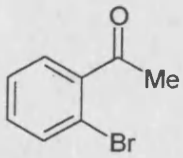

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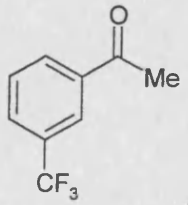

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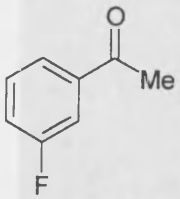

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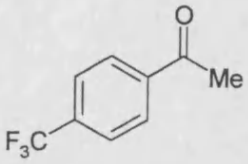

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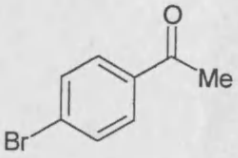

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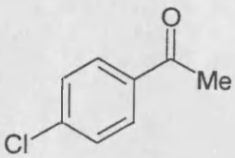

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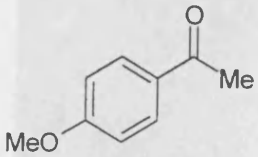

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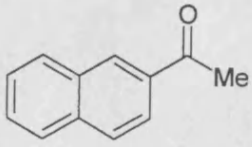

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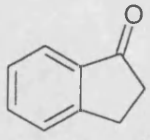

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